Primary Snoring in Children:

Epidemiology, Complications and Natural History

ZHU, Yin

Supervisor: Prof. Albert Martin Li

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Abstract of thesis entitled:

Primary Snoring in Children: Epidemiology, Complications and Natural History

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Objectives

To investigate (1) prevalence of snoring in preschool and school-aged children in Hong Kong; (2) complications of childhood primary snoring (PS); (3) natural history of childhood PS.

Methods

(1) Prevalence of snoring in Chinese children: Two population-based surveys were performed in 21 kindergartens and 32 primary/secondary schools respectively.

(2) Complications of childhood PS: Neurocognitive function, 24-hour ambulatory blood pressure (ABP), endothelial function and polysomnography (PSG) were performed.

(3) Natural history of PS in children: Children diagnosed as PS in our previous epidemiology study were invited to repeat PSG at 4-year follow-up.

Results

(1) Prevalence of snoring in Chinese children: The prevalence rate of habitual snoring was 5.5% in preschool children and 9.2% in school-aged children respectively.

(2) Complications of childhood PS: No significant impairment in all the neurocognitive functioning tests was found in children with PS compared to non-snoring children. Sky Search DT score was negatively associated with the increase in severity across the sleep-disordered breathing spectrum from non-snoring control, to PS, to obstructive sleep apnoea (OSA), adjusted for age, gender and parental socio-economic status. In pubertal teenagers, PS subjects had significantly higher adjusted percentage of stage 1 sleep and wakefulness after sleep onset compared to healthy controls. After adjustment for age, gender, BMI z-score and parental hypertension, habitual snoring was not associated with any ABP values. PS cases had significantly lower flow-mediated vasodilation than non-snoring controls after adjustment.

(3) Natural history of PS in Children: Seventy children with a mean age of 14.7±1.8 years were analysed in this follow-up study. At follow-up, 26 subjects (37.1%) progressed to OSA. Persistent overweight/obesity was an independent risk factor for the development of OSA at follow-up.

Conclusions

Habitual snoring is a common problem in Hong Kong Chinese children. Childhood PS is related to endothelial dysfunction, and sleep architecture is altered in pubertal adolescents with PS. A trend towards adverse attention

exists in children with PS. If left untreated, more than one third of PS subjects may progress to OSA over a 4-year follow-up period, especially those who are persistently obese. Therefore childhood PS may not be considered as totally benign.

摘要

目的：

研究 1）香港幼稚園兒童和中小學學生中鼻鼾的發生率；2）兒童原發性鼻鼾症的併發症及 3）自然史。

方法：

（1）香港幼稚園兒童和中小學生中鼻鼾的發生率：這是一項以社區為基礎的調查，分別在 21 間幼稚園和 32 間中小學中進行。

（2）兒童原發性鼻鼾症的併發症：研究涉及神經認知功能、24 小時動態血壓、內皮細胞功能及多導睡眠儀檢測。

（3）兒童原發性鼻鼾症的自然史：曾經診斷為原發性鼻鼾症的兒童在 4 年后再次接受多導睡眠檢測儀測試。

結果：

（1）香港幼稚園兒童和中小學生中鼻鼾的發生率：習慣性鼻鼾在幼稚園和中小學生中的發生率分別為 5.5%和 9.2%。

（2）兒童原發性鼻鼾症的併發症：原發性鼻鼾症兒童與正常對照組相比，所有的神經認知功能都沒有明顯差別。Sky search DT 分數在控制了年齡、性別和父母社會經濟地位后，隨著睡眠障礙疾病譜的嚴重程度的升高而下降。在青春發育期的青少年中，原發性鼻鼾症組比正常對照組有更高的調整后 1 期睡眠百分比和

睡眠后覺醒百分比。在調整年齡、性別、體質指數 z 分數和高血壓家族史后，習慣性鼻鼾與動態血壓無顯著關係。原發性鼻鼾症組的血管扩张反应在調整了混淆因素后比正常對照組更低。

（3）兒童原發性鼻鼾症的自然史：共分析了 70 名平均年齡 14.7±1.8 歲的兒童。在隨訪時，26 例（37.1%）進展成阻塞性睡眠呼吸暫停症。持續性過重/肥胖是一個與原發性鼻鼾症進展為阻塞性睡眠呼吸暫停症相關的危險因素。

結論

習慣性鼻鼾是香港華裔兒童及青少年中的常見問題。原發性鼻鼾症與內皮細胞功能受損有關。青春發育期青少年的原發性鼻鼾症對睡眠結構有影響。注意力在兒童原發性鼻鼾症中有變差的趨勢。如果不治療，超過三分之一的原發性鼻鼾症兒童在 4 年後進展成阻塞性睡眠呼吸暫停症，特別是持續肥胖者。因此原發性鼻鼾症不完全是良性的。

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CHAPTER 1

GENERAL INTRODUCTION

Snoring is a breathing sound or noise which originates during sleep. It typically appears during the inspiratory phase of the respiratory cycle, even though a small expiratory component can also be heard sometimes.[1] The American Sleep Disorders Association (ASDA) defined snoring as “Loud upper airway breathing caused by vibrations of the pharyngeal tissues”.[2]

As self-reported snoring is highly subjective, there is a need for an accurate definition of snoring in terms of objective measurement. Therefore researchers have been inspired to utilize acoustic measurements to try to quantify and standardize the features of snoring sounds, relating its intensity, timing (continuous or interrupted), duration, frequency etc.[1] However it is not easy to define the characteristics of snoring, as it comprises a sound spectrum ranging from modest audible breathing to loud vibratory sounds that are readily perceived as “snoring” by human observers.[3] Moreover snoring is not a homogeneous acoustic phenomenon, as it changes in the course of the sleep period and may vary from night to night. It can be influenced by many factors such as the sites of upper airway narrowing,[4] the route of breathing (oral and/or nasal),[5] body position[6] etc.

Overall for the beholder it is quite obvious to discern snoring from other breathing sounds such as stridor and wheeze. However, objective parameters defining these sounds as “snoring” are lacking so far.[7]

1.1 Pathogenesis of Snoring

1.1.1 The Upper Airway

The upper airway extends from the lips and nostrils to the vocal cords.[1] The structure of the upper airway consists of bones including the nasal turbinates, maxilla, mandible, hyoid, cervical vertebrae, and soft tissues including adenoid, tonsils, soft palate, uvula, pharyngeal muscles, epiglottis, tongue, pharyngeal fat pad and mucosa.[8]

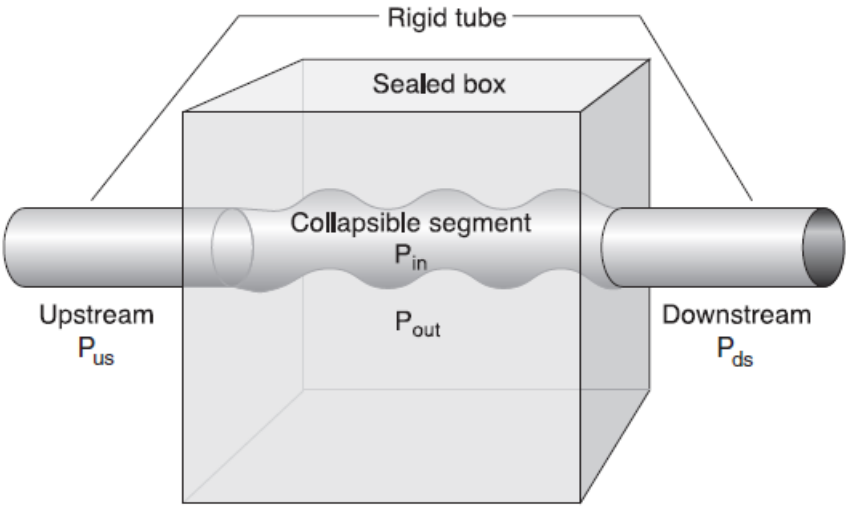
In general, the upper airway is divided into three segments: 1) The proximal segment is the nasal cavities and rhinopharynx. It has an osseous-cartilaginous structure and is rigid and not collapsible under the effect of the inspiratory pressure; 2) The middle segment is the oropharynx, a typical collapsible structure which can decrease its cross-sectional area with the approach of the walls under sufficient inspiratory negative pressure; 3) The distal segment is the larynx, also a cartilaginous and rigid structure which is not prone to collapse under normal circumstances. The upper airway can therefore be thought of as a tube that is rigid at both ends but flexible in its mid section.[1]

A Starling resistor model which consists of a collapsible tube with a sealed box interposed between two rigid segments has given some insight regarding the mechanical properties of the upper airway (Figure 1).[9] In this model, the collapsible segment of the tube is bound by an upstream and downstream segment with corresponding upstream (Pus) and downstream pressures (Pds). Pus is atmospheric at the airway opening, and Pds is the tracheal pressure. The critical closing pressure (Pcrit) of the passive airway is defined as the pressure inside the airway at which the airway collapses. The pressure gradient during airflow through the system is defined by Pus -

Pcrit and remains independent of Pds. Therefore with increasing Pcrit, as the difference between Pus and Pcrit decreases, inspiratory airflow limitation with eventually develop, and when the Pus falls below Pcrit, complete airway occlusion occurs.[10]

The increase in Pcrit can be caused by elevated collapsing pressures on the airway, usually associated with inactivity of pharyngeal dilator muscles, mass of the soft tissues surrounding the airway or deformity of the supporting bony structures which reduce the cross-sectional area of the airway. In addition, the enlargement of soft tissues inside the upper airway can also lead to its occlusion.[10]

Figure 1.1. Starling resistor model of upper airway



1.1.2 The Generation of Snoring Sound

Sleep is a requirement for the appearance of snoring. The most important effect of sleep is the decrease of the tone of the dilator muscles of

the upper airway, which causes increasing resistance and provoke a flow limitation.[11] The following simultaneous factors are necessary to produce snoring: 1) sleep; 2) reduction of cross-sectional area of the upper airway; 3) vibrating structures which are usually pharyngeal soft tissues behaving like a Starling resistor; and 4) thorax bellows which act with suction inspiratory pressure.[1]

All in all, the source of the snoring sound is the oropharyngeal segment of the upper airway. Relative atonia of the upper airway dilator muscles during sleep induces narrowing and increased resistance at this level. As a result, airflow becomes turbulent and the pharyngeal tissues vibrate as the air passes through. More specifically, snoring is characterized by oscillations of the soft palate, pharyngeal walls, epiglottis and the tongue.[3]

1.1.3 Predisposing Factors

The main predisposing factors of snoring in children include:

(1) Adenoid and tonsillar hypertrophy. This is an important cause of obstruction of upper airway especially in children aged 4- to 8 years.[12-14]

(2) Obesity. Obesity is a predisposing factor for snoring in children because of the mass loading of soft tissues surrounding the upper airway such as the fat pads, soft palate, pharyngeal wall and tongue as well as impaired ventilatory control.[15]

(3) Nasal obstruction. Factors associated with nasal obstruction such as rhinitis, sinusitis and allergies may aggravate snoring by increasing the negative intrapharyngeal pressure and facilitating the conditions leading to inspiratory flow limitation.[16]

(4) Abnormal craniofacial growth. In particular, patients with bimaxillary or mandibular retrognathia with a receded chin are more prone to develop snoring.[17]

(5) Neuromuscular disorders. Duchenne muscular dystrophy and cerebral palsy predispose children to have snoring as a result of the already weakened dilator muscles of the upper airway.[13]

1.2 Pathophysiology of Snoring

Once snoring develops, recurrent vibration of the air column in the upper airway can induce mechanical trauma. This recurrent vibratory trauma will in turn promote the development of an inflammatory response leading to mucosal swelling and subsequently to upper airway obstruction.[18] A study showed that vibration enhances interleukin-8 release in a cell model of snoring-induced airway inflammation.[19] Although the evidence supporting such mechanical process is currently unavailable in children, the up-regulation of leukotriene receptor expression was present in lymphadenoid tissues of children with sleep apnoea, and anti-inflammatory therapy was an alternative treatment regimen in such children.[20-22] Additionally, muscular and nervous fibers lesions of pharyngeal muscles due to the mechanical effects of the vibration in heavy snorers could be found,[23] which would also further impair the activity of the dilator muscles maintaining the patency of upper airway.

Moreover tissue vibration was demonstrated to induce carotid artery endothelial dysfunction in a rabbit model, suggesting a direct plausible mechanism linking snoring to the development of carotid atherosclerosis.[24]

1.3 Habitual Snoring in Children

Habitual snoring usually refers to snoring every night or every other night.[13] In most of the studies in children, snoring frequency ≥3 nights/week based on parent-reported questionnaire was used to define habitual snoring.[25-27] It is a common problem which can occur at any age, from infants, toddlers, school-aged children to adolescents. The prevalence rates of habitual snoring in children worldwide and associated risk factors are shown in Table 1.1. The wide discrepancy of the prevalence may be attributed to different definitions used for habitual snoring, different races and different age groups. The most common risk factors for developing habitual snoring in children included male gender, obesity, allergic diseases, adenotonsillar hypertrophy, household passive smoking, African-American race and lower socioeconomic status. Our research group has carried out a population-based survey on habitual snoring in children aged 6-13 years and reported a prevalence rate of 7.2% in Hong Kong.[26] Nevertheless local data are still lacking on prevalence of snoring in preschool children and adolescents.

It has been found that parent-reported habitual snoring is associated with neurocognitive consequences in children. Accumulating cross-sectional research studies showed that children with habitual snoring were at higher risk for having neurobehavioral problems than non-snoring subjects, including poor academic performance,[25, 28-31] hyperactivity,[28, 32, 33] inattention,[32, 34] daytime sleepiness,[25, 34, 35] anxious/depressed mood,[36] emotional reactivity problems,[34, 36] and intelligence deficits.[37]

Table 1.1 Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
>=3 nights/wk	457	Australia [38]	1wk-14wk	9							+	-	-	
Yes/no	1,585	New Zealand[39]	1mo-6mo	26.1	Older age	Male					+	+		
Yes/no	200	Russia[40]	2mo–4mo	5										
>=3 days/wk	944	US[41]	2wk-2yr	5.3	-	-							African-American	
>=3 nights/wk	681	US[42]	1yr	15								-	African-American	
Always or often	1,471	Finland[43]	1yr-6yr	6.3	-	-		+			+	+		
NA	985	Turkey[44]	3yr-6yr	7.6		Male								
>=3 nights/wk	1,844	Sweden[45]	5yr-7yr	7.7		Female					+			
Always or often	595	Italy[46]	2yr-8yr	34.5	-	-	-				+	-		
More than half the time	346	US[47]	2yr-6yr	13.9	-	-	-		-				African-American	-
Often	190	France[48]	5yr-6yr	10		-		+	+	-		-		-

(Continued) Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
>=4 nights/wk	974	Australia [49]	2yr-6yr	10.5	-	-	-		+					
Almost always	6,742	UK[50]	1yr-4yr	7.9	Older age	Male	-	+	+	+	+	+	White but not South Asian	+
>=3 nights/wk	23,481	Asia Pacific[51]	0yr-3yr	Different across countries		Male							White	
Most nights	782	England [52]	4yr-5yr	12.1										
>=4 nights/wk	4,980	Australia [53]	4yr-5yr	9.4										
>3 nights/wk	11,114	Singapore [54]	4yr-7yr	6.0		Male	+	+	+	+		+	Malays	
>=3 nights/wk	3,019	US[55]	5yr	12		Male								
Every night	325	Sweden[56]	4yr	6.2							+			
>=3 nights/wk	378	Sweden[57]	5yr-6yr	5										
>=3x/wk	1,010	US[25]	3yr-5.3yr	22.0	-								African-American	+

(Continued) Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
>4 nights/wk	16,321	US[58]	5yr-7yr	11.3	-	-		+	+			+	African-American	
>=3 nights/wk	635	Sweden [59]	6yr–8yr	9.3										
Frequently or almost everyday	1,164	Turkey[28]	7yr-13yr	3.5	Young age	Male	+	+			+	+		-
Frequently or almost always	20,152	China[60]	5yr-12yr	12.0	Peak age 7yr	Male	+	+	+			+		+
Yes/No	652	Belgium [61]	6yr-12yr	32.6				+	+*					
>=3 nights/wk	6,349	Hong Kong[26]	5yr-14yr	7.2	Peak age 6yr-7yr	Male	+	+	+	-	+	-		-
>=6 nights/wk	3,047	Hong Kong[62]	6yr-12yr	10.9		Male		+						
Often or always	2,147	Turkey[63]	5yr-13yr	7.0	Peak age 11yr-13yr	Male			+		+	+		

(Continued) Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
Everyday	1,211	Turkey[64]	6yr-13yr	2.4										
Always or often	806	US[65]	6yr-12yr	15.1	-	Male		+						
Frequently or always	1,129	Germany [66]	9.6± 0.7yr	10.0	-	-	+				-	-		+
Yes/No	1,404	Sweden [67]	6yr-11yr	23.0										
Most nights	1,008	Thailand [68]	6yr-13yr	8.5	-	-	-	+				-		
Often	1,615	Italy[69]	6yr-13yr	7.3	Young age	-		+	-			+		
Frequently	976	Portugal [70]	6yr-11yr	8.6	-	-					+			
>=4 nights/wk	996	Australia [71]	4yr-12yr	15.2	Young age	-		+	+			+		
Frequently	998	Brazil [72]	9yr-14yr	27.6								+		
At least some nights	473	US[74]	3yr-14yr	22.9	Peak age 3yr-6yr		-	+	-					

(Continued) Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
>3 nights/wk	1,198	Turkey[75]	3yr-11yr	3.3		-		+	-			+		
Always	895	Italy[76]	3yr-11yr	4.9		Male								
Yes/No	909	Nigeria[77]	3yr-16yr	34.2	Peak age 3yr-6yr	-								-
Always	3,680	Greece [78]	1yr-18yr	4.2	-	Male		+				+		
>=2 nights/wk	1,650	Australia [79]	0yr-17yr	14.2	-	Male	+		+				-	-
Often or very often	454	Iceland[80]	6mon-6yr	3.2		Male						-		
Frequently or almost always	1,481	US[81]	4yr-11yr	10.5	-	-							Hispanic	
>=3 nights/wk	14,883	China[82]	<5yr	4.4	Young age	Male								
Often	1,784	Turkey[12]	4yr-17yr	4.1										+
Often	2,209	Italy[83]	10yr-15yr	5.6	Older age	Male	+	+	-			+		+

(Continued) Published community-based studies on prevalence and risk factors of habitual snoring in children

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
Every or nearly every night	1,014	US[84]	13yr-16yr	6										
>=3 nights/wk	3,871	Korea[27]	15yr-18yr	11.2		-	+					+		
Often or always	1,030	Turkey[85]	12yr-17yr	4.0	Young age	-	+	+				+		
Very often	332	Austria[86]	11yr-15yr	2.1										
Often or every night	24,682	France[87]	15yr-20yr	4.8	-	Male	+					+**		
>=3 nights/wk	2,900	Iran[88]	11yr-17yr	7.9		Male			+					
Sometimes or often	245	UK[89]	<10yr	27	Peak age 4yr-5yr and 8yr-9yr					+	+	+		

NA, not available; AR, allergic rhinitis; URI, upper respiratory tract infection; SES, socio-economic status.
*wheezing
**active smoking

1.4 Snoring and Childhood Obstructive Sleep Apnoea (OSA)

Snoring is the most common symptom in children with obstructive sleep apnoea (OSA), which is at the severe end of the sleep-disordered breathing (SDB) spectrum.[90, 91] OSA refers to recurrent episodes of partial or complete upper airway obstruction during sleep, usually accompanied by intermittent hypoxia and sleep fragmentation.[92] Other nighttime manifestations suggesting OSA include mouth breathing, sweating, sleeping in prone position, enuresis, restless sleep and so forth.[93] Childhood OSA must be confirmed by the respiratory event-related parameters generated from polysomnography (PSG), although its diagnostic criteria have not been standardized. Obstructive apnoea hypopnea index (OAHI)≥1, ≥1.5, ≥3, ≥5 and obstructive apnoea index (OAI)≥1have been used as cut-offs for OSA.[94] According to the International Classification of Sleep Disorders version II (ICSD-2), children are diagnosed as OSA if having (1) habitual snoring, (2) at least one more OSA-related symptom, and (3) OAHI≥1.[95] Using this criterion, our research group reported an OSA prevalence of 4.8% for Hong Kong primary school-aged children. Male gender, obesity and increased adenoid and tonsil size were independent risk factors associated with presence of OSA.[94]

1.4.1 Clinical Complications of Childhood OSA

Based on the latest review in 2012,[96] childhood OSA is related to a large array of sequelae.

1.4.1.1 Neuropsychological and Cognitive Morbidities of OSA

Around 40 articles directly explored the relationship between OSA and cognitive or neuropsychological deficits over the last 10 years. Almost all demonstrated cognitive deficits or behavioral abnormalities in association with the diagnosis of OSA.[96] The types of neurocognitive deficits involve general intelligence,[97-99] academic performance,[100-102] executive function,[97, 99, 103] learning and memory skills,[101, 104-107] language/verbal skills[102, 108-112] and attention.[97, 101, 106, 113-116] Hyperactivity and/or Attention-deficit/hyperactivity disorder (ADHD) symptoms were the most commonly studied and reported behavioral abnormalities associated with OSA.[113, 114, 117-120] Somatization, depression,[112, 114, 118, 121, 122] behavior problems,[115, 116, 119-128] aggression, social problems[114, 116, 118, 129] and excessive daytime sleepiness[81, 102, 130, 131] were the other most frequently reported behavioral abnormalities.

It is thought that intermittent hypoxia and/or hypercapnia as well as sleep disruption are the pathophysiological mechanism of OSA responsible for adverse daytime neurobehavioral function. They are suspected to cause prefrontal cortical dysfunction and lead to impaired cognitive execution.[132] Intermittent hypoxia is a well-known contributor to general intellectual deficits in adult OSA.[133] In animal models, intermittent hypoxia induces substantial increases in neuronal cell loss and adversely affects spatial memory tasks.[134] Several aforementioned studies indeed have shown a correlation between different PSG indices representing hypoxia and arousals and cognitive and behavioral outcomes.[101, 116, 130, 135]

There were approximately 20 studies examining the changes in behavior and/or cognition after surgical treatment of OSA. The majority of investigations showed agreement about post-treatment improvement of behavior,[115, 120, 123-125, 127, 128, 136] quality of life,[123, 127, 137-141] and hyperactivity and/or ADHD[114, 115, 118, 120, 121, 137] by using subjective questionnaire. Several studies have demonstrated improved intelligence, attention, memory and analytic thinking by using objective measurement after treatment of OSA.[99, 111, 137]

In summary, these studies suggest that, in developing children, early diagnosis and treatment of paediatric OSA may improve their long-term cognitive and social potential and school performance.

1.4.1.2 Cardiovascular Morbidities of OSA

A large number of studies found that cardiovascular changes can occur in the presence of OSA in children. Studies using more sophisticated techniques have demonstrated subclinical evidence of cardiac dysfunction, with an effect on both the right and lift ventricles.[142-146] OSA in childhood has also been shown to exert an effect on both systolic and diastolic blood pressure (BP). A correlation was demonstrated between the severity of OSA and indices of elevated BP.[147-152] In addition, several studies suggest that childhood OSA can affect autonomic regulation, such as decreased heart rate variability and tachycardia.[153-155] These studies suggest that childhood OSA may jeopardize long-term cardiovascular health. Oxidative stress and sympathetic overactivity

caused by OSA are proposed mechanisms linking OSA and cardiovascular consequences.[15]

1.4.1.3 Metabolic Morbidities of OSA

In children, studies examining the relationship between OSA and glucose/insulin homeostasis have yielded conflicting results. Several research groups have demonstrated an independent and positive correlation between the severity of OSA and insulin resistance in obese children and adolescents,[156-162] and *Gozal et al* documented a significant reduction in insulin level after adenotonsillectomy in obese children.[163] However, this positive association was not supported by studies involving prepubertal or non-obese children.[164-166] Besides, resolution of OSA following adenotonsillectomy[167, 168] or continuous positive airway pressure (CPAP) therapy[169] did not have any significant influence on markers of glucose and insulin metabolism. Our data using oral glucose tolerance test (OGTT) also showed that childhood OSA had no independent effect on glucose tolerance or insulin sensitivity after adjustment for obesity, pubertal stage and sleep architecture parameters (unpublished). The relationship between OSA and glucose metabolism in children thus remains undefined.

1.4.2 Treatment of Childhood OSA

According to the updated guideline for management of childhood OSA recommended by the American Academy of Pediatrics,[96] adenotonsillectomy

(AT) remains the primary treatment. Although OSA improved postoperatively, the proportion of patients who had residual OSA ranged from 13% to 29% in low-risk populations to 73% when obese children were included. Nevertheless OSA may improve after AT even in obese children, thus supporting surgery as a reasonable initial treatment. CPAP is effective in the treatment of OSA, but compliance is a major barrier. For this reason, CPAP is not recommended as first-line therapy for OSA when AT is an option. Intranasal steroids may ameliorate mild OSA, but follow-up is required. Evidence was insufficient to recommend rapid maxillary expansion.

1.5. Primary Snoring in Children

1.5.1 Definition of Childhood Primary Snoring (PS)

In contrast to OSA, primary snoring (PS) refers to snoring without apnoea, frequent arousals or gas exchange abnormalities.[170] Although >95% of the patients with OSA presented habitual snoring,[171] not all the children with snoring would have OSA. It has been verified that PS can not be reliably distinguished from OSA by clinical symptoms alone.[172] In adults, acoustic analysis of snoring has recently been carried out to try to identify the degree as well as the site of obstruction of the upper airway.[3] Such studies, however, have rarely been conducted or reported in children. Hence the gold standard for the differentiation between PS and OSA is still nocturnal PSG. In spite of the not well established agreement of diagnostic criterion for childhood PS, the most commonly used definition is history of snoring plus OAHI<1.[173-176]

1.5.2 Clinical Complications of Childhood PS

PS has been positioned at the milder end of the SDB severity continuum,[177] and treatment is usually not prescribed.[178] Nevertheless, whether deferment of treatment of PS is safe arouses controversy recently. It remains unresolved whether c0068ildren with PS would also have adverse complications. Because PS, in spite of the absence of apnoea or hypopnoea during sleep, is resulted from the reduction of cross-sectional area and partial occlusion of the upper airway, hypoxia and possible secondary subtle sleep disturbance may still occur and it is supposed to be a different entity from non-snoring subjects. Thereby we hypothesized that children with PS were also at increased risk of developing clinical morbidities. However the majority of the previous studies recruited PS children to serve as a control group against OSA patients, and few of them focused on the comparisons between PS and non-snoring children. The existing evidence suggested that children with PS had neurocognitive and behavioral impairments, BP elevation and endothelial dysfunction (Table 1.2). Therefore PS should no longer be considered as completely benign.[179] The mechanism of the demonstrated morbidities resulted from PS is not clear, because PS is normally not accompanied by oxygen desaturation. However researchers assumed that PS might be associated with subtle hypoxia and/or electroencephalograph (EEG) changes which could not be detected by the conventional techniques.[174]

Table 1.2 Previous studies on the clinical complications of childhood primary snoring compared with non-snoring controls

Author	Year	Definition of PS	Sample size	Age	Results
Gozal D et al[131]	2001	Snoring +AI≤2	14 PS, 24 healthy controls, 54 OSA	7.3±0.8 years	Mean sleep latencies were not significantly different between PS and normal control group using MSLT.
Kwok KL et al[173]	2003	Snoring +OAHI≤1	30 PS, 30 healthy controls	9.5±2.8 years	Children with PS had increased daytime BP and reduced arterial distensibility.
O'Brien LM et al[180]	2004	Snoring +OAI<1 +AHI<5 +SpO_2 nadir>90% +peak $P_{ET}CO_2$ <50 mmHg +ArI<20	87 PS, 31 healthy controls	5-7 years	PS associated with worse attention, social problems, anxious /depressive symptoms and lower cognitive abilities, language and visuospatial functions.
Beebe DW et al[97]	2004	Snoring +AHI<1	17 PS, 17 healthy controls, 15 OSA	6-12 years	Impairments was found on measures of behavior regulation and some aspects of attention and executive functioning in PS.
Hamasaki Uema SF et al[106]	2007	N/A	37 PS, 20 healthy controls, 24 OSA	6-12 years	PS showed worse performance on learning and memory.

(Continued) Previous studies on the clinical complications of childhood primary snoring compared with non-snoring controls

Author	Year	Definition of PS	Sample size	Age	Results
Li AM et al[175]	2009	Habitual snoring +OAHI<1 +ODI<1 +SpO_2 nadir≥90%	46 PS, 56 healthy controls, 88 OSA	6-13 years	Nighttime diastolic BP was significantly higher in the children with PS compared with controls after adjusting for age, sex, and BMI.
Jackman AR et al[181]	2010	Snoring +OAHI<1	60 PS, 37 healthy controls, 56 OSA	3-5 years	PS was associated with poorer behavior but not cognitive performance.
Biggs SN et al[182]	2011	Snoring +OAHI <1 and normal CO_2 and SpO_2	55 PS, 34 healthy controls, 38 OSA	7-12 years	Working memory deficits at PS was found compared to normal controls.
Bourke R et al[183]	2011	Snoring +OAHI<1	59 PS, 35 healthy controls, 43 OSA	7-12 years	PS had lower general intellectual ability and higher rates of impairment in executive and academic functioning.
Bourke R et al[184]	2011	Snoring +OAHI<1	57 PS, 35 healthy controls, 42 OSA	7-12 years	Behavioral, attention, and executive function difficulties were present in children with PS.
Miano S et al[185]	2011	Habitual snoring +AHI<1 +microphone-detected snoring	13 PS, 60 healthy controls, 31 OSA	8.6±1.9 years	The IQ estimates of PS and OSA were lower and the ADHD rating scale scores higher than those of controls.

(Continued) Previous studies on the clinical complications of childhood primary snoring compared with non-snoring controls

Author	Year	Definition of PS	Sample size	Age	Results
Brockmann PE et al[186]	2012	Habitual snoring +OAHI<1 +RDI<1 +ODI<4	69 PS, 410 healthy controls, 23 UARS/OSA	9.6±0.7 years	Compared to non-snoring controls, children with PS had more hyperactive and inattentive behavior, poor school performance. Consequences were similar to those associated with UARS or OSA.
Li AM et al[174]	2012	Habitual snoring +OAHI<1	73 PS, 128 healthy controls	6-18 years	PS is associated with reduced FMD, independent of obesity.

AI, apnoea index; PS, primary snoring; OSA, obstructive sleep apnoea; MSLT, multiple sleep latency test; OAHI, obstructive apnoea hypopnoea index; BP, blood pressure; OAI, obstructive apnoea index; AHI, apnoea hypopnoea index; $P_{ET}CO_2$, end-tidal carbon dioxide pressure levels; ArI, arousal index; SpO_2 nadir, oxygen saturation nadir; ODI, oxygen desaturation index; IQ, intelligence quotient; ADHD, attention deficit hyperactivity disorder; BMI, body mass index; RDI, respiratory disturbance index; UARS, upper airway resistance syndrome; FMD, flow-mediated vasodilation.

1.5.3 Natural History of Childhood PS

Another poorly defined but important issue is that whether PS will progress to OSA, persist or resolve over time if left untreated. As is mentioned before, recurrent vibratory trauma resulting from snoring will promote an inflammatory response leading to mucosal swelling, together with the nervous fibers lesions affecting the activity of pharyngeal dilator muscles. Therefore we hypothesized

that PS would worsen and progress to OSA over a period of time if snoring persisted.

To our knowledge, only three research studies that examined the natural history of PS in children have been published. The three studies repeated polysomnography (PSG) in cohorts of 20, 9 and 31 children with PS over a 2-year, 3-year and 6-month period respectively.[176, 187, 188] All three studies concluded that PS in children generally did not evolve to OSA over time (Table 1.3). These studies, however, had small sample size and consisted of hospital-based subjects.

Table 1.3 Previous studies on the natural history of primary snoring in children

Author	Year	Definition of PS	Initial age	Sample size	Follow-up period	Results
Marcus CL et al[176]	1998	Snoring +OAI≤1 +SpO_2 nadir >90% + peak $P_{ET}CO_2$ ≤53 mmHg or hypoventilation ($P_{ET}CO_2$ ≥50 mmHg) for <10% of total sleep time	6±4 years	20	2 years	No significant changes in PSG indicies were found over the follow-up period.
Topol HI et al[188]	2000	Snoring +normal findings on PSGs	7.7±2.2 years	9	3 years	
Nieminen P et al[187]	2001	Snoring +OAHI<1	6.0±1.8 years	31	6 months	

1.6 Aims of the study

In this thesis, we aimed to examine various issues related to snoring, especially PS in children, including (1) the prevalence of snoring and its associated risk factors in preschool, primary and secondary school children in Hong Kong; (2) the neurocognitive and cardiovascular complications of PS; and (3) the natural history of PS and risk factors associated with its progression to OSA.

CHAPTER 2

Prevalence of Snoring in Chinese Pre-school Children

2.1 INTRODUCTION

Snoring is a low-frequency sound produced by vibrations of the soft tissues in the oropharynx during sleep.[189] It is the most common manifestation of sleep-disordered breathing (SDB), with severity ranging from primary snoring to obstructive sleep apnoea (OSA).[90] In children, habitual snoring (HS) has been demonstrated to be associated with a variety of clinical sequelae even in the absence of sleep apnoea or hypopnoea, including impaired neurobehavior, poor academic performance,[31, 37, 186] elevated blood pressure,[175] and reduced endothelial function.[174] In addition, several studies have shown that habitual snorers have significantly more sleep problems, such as parasomnia, restless sleep, sleep-onset delay and night awakenings.[26, 43, 46]

HS can occur at any age from infancy to adolescence, with the reported prevalence ranging from 2.4% to 34.5%.[38, 46, 64, 85] However relatively few data is available for preschool children, and almost all published studies were carried out in western countries (Table 2.1). The prevalence rate of HS in preschool children in Hong Kong has never been reported. A variety of risk factors have been demonstrated to be associated with HS in preschoolers. Several studies demonstrated a positive relationship between HS and male gender,[50, 54, 55] obesity,[54] allergic rhinitis,[43, 50, 54] asthma,[50, 54] exposure to environmental

tobacco smoke (ETS),[43, 50, 54] and low socioeconomic status,[25, 50] however these positive associations were not consistent across all studies.[46-49]

In addition, the assessment for ETS exposure in all previous publications was based on parent-completed questionnaires. Hence there is a possibility of under-reporting by parents who smoke. An objective indicator is therefore needed to enhance the reliability when assessing ETS exposure. Cotinine, a major degradation product of nicotine metabolism, is an important biochemical marker for quantifying passive exposure to cigarette smoke.[190] In this study urine cotinine which is a non-invasive method widely used in epidemiologic studies was utilized to examine ETS exposure.

In this study, by using a population-based sample, we aimed to determine (1) the prevalence of HS, (2) its associated risk factors, and (3) its related sleep problems in preschool Chinese children.

Table 2.1 Published community-based studies on prevalence and risk factors of HS in preschool children

Definition of habitual snoring	Sample size	Location	Age range	Prevalence, %	Risk factors of habitual snoring								
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Low SES
Most nights	782	UK[52]	4yr-5yr	12.1									
>=4 nights/wk	4,980	Australia [53]	4yr-5yr	9.4									
Always or often	1,471	Finland [43]	1yr-6yr	6.3	-	-		+			+	+	
NA	985	Turkey[44]	3yr-6yr	7.6		Male							
>=3 nights/wk	1,844	Sweden [45]	5yr-7yr	7.7		Female					+		
Always or often	595	Italy[46]	2yr-8yr	34.5	-	-	-				+	-	
More than half the time	346	US[47]	2yr-6yr	13.9	-	-	-		-				-
Often	190	France[48]	5yr-6yr	10		-		+	+	-		-	-
>=4 nights/wk	974	Australia [49]	2yr-5yr	10.5	-	-	-		+				
Almost always	6,742	UK[50]	1yr-4yr	7.9	Older age	Male	-	+	+	+	+	+	+
>=3 nights/wk	11,114	Singapore [54]	4yr-7yr	6.0		Male	+	+	+	+		+	

(Continued) Published community-based studies on prevalence and risk factors of HS in preschool children

Definition of habitual snoring	Sample size	Location	Age range	Prevalence, %	Risk factors of habitual snoring								
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Low SES
>=3 nights/wk	3,019	US[55]	5yr	12		Male							
Every night	325	Sweden[56]	4yr	6.2							+		
>=3 nights/wk	378	Sweden[57]	5yr-6yr	5									
>=3 nights/wk	1,010	US[25]	3yr-5yr	22.0	-								+

NA=not applicable
AR, allergic rhinitis; URI, upper respiratory tract infection; SES, socio-economic status.

2.2 METHODS

2.2.1 Study Population

Healthy Chinese preschool children aged 2-6 years who are Hong Kong permanent residents were eligible for inclusion. Subjects were excluded from the study if they were reported by their parents to have cardiovascular, renal or neuromuscular diseases or chromosomal abnormalities, or if they had previously undergone upper airway surgery.

Based on our pilot study carried out in a randomly chosen kindergarten, 4.9% (10 out of 205) of children had HS. Assuming the maximum error of estimate was 1%, the minimum sample size with 95% confidence needed for a population prevalence was 1,790 children. [191]

All kindergartens registered under the Education Bureau (http://www.edb.gov.hk/index.aspx?nodeID=480&langno=2) were stratified according to the four geographic regions in Hong Kong and were randomly recruited in proportion to childhood population of the respective region according to 2006 population by-census statistics (http://www.censtatd.gov.hk/hong_kong_statistics/dashboard/index_en_GHS.html). All subjects were recruited within class as a clustered randomised sampling frame. Consequently a total of 21 kindergartens participated. Sleep survey questionnaires (see below) were delivered to parents of 2,954 children. Informed written consents were obtained from subjects' parents. Approval by the ethics committee of the Chinese University of Hong Kong was obtained.

2.2.2 Questionnaires

An expanded version of a validated sleep pattern and symptom questionnaire[51] was completed by parents of recruited subjects (Appendix 1). The questionnaire included specific questions on sleep patterns, sleep-related behaviours, as well as age, gender and socioeconomic factors. The question on snoring was “Does your child snore when he/she is asleep?” and the options given were “never”, “only when he/she suffers from cold or allergy”, “sometimes” and “frequently”. For the participants who chose the latter two options, a drop-down list of frequencies was then provided. We defined habitual and occasional snoring as snoring ≥3 nights per week and 1-2 nights per week, respectively. Non-snorers were defined as those reporting “never” or “only when he/she suffers from cold or allergy”. The respondents were asked to describe their child’s behaviour during the last two weeks.

The Chinese version of modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires were also given to parents of consented children (Appendix 2). The modified ISAAC questionnaire asked for information on demography, asthma, rhinitis and eczema, together with various possible risk factors, including family history of atopic diseases, environmental tobacco smoke (ETS) exposures, pet ownership and etc.[192]

2.2.3 Anthropometry Assessment

At each participating kindergarten, a team of research assistants conducted on-site weight and height measurements. The weight of subjects

was measured bare-footed by the electronic scale and standing height by Harpenden stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and were converted to z-scores appropriate for age and gender, according to local reference.[193]

2.2.4 Measurement of Urinary Cotinine

One third of children who completed both questionnaires were randomly selected to provide urinary sample for cotinine analysis. The sample was collected on-site by our researchers. Urine was stored at -20^{o}C until analysis for cotinine by enzyme-linked immunosorbent assay (Calbiotech, Spring Valley, CA). The detection limit of this assay was 1ng/mL. The inter-assay coefficients of variation were < 6%. Urine cotinine concentrations were corrected for creatinine (Cr), which was measured by modified Jaffe reaction (Roche Diagnostics GmbH, Mannheim, Germany). Increased urinine cotinine was defined as urinary cotinine concentrations≥30ng/mgCr.[194]

2.2.5 Statistical Analyses

Data were presented as mean (standard deviation), median (interquartile range) and percentages for parametric, non-parametric and categorical data, respectively. The prevalence of HS, occasional snoring and non-snoring and their 95% confidence interval (CI) were calculated.[191] The trends of characteristics across snoring frequency groups were analysed using analysis of variance (ANOVA) tests for continuous variables and linear-by-linear

association χ^2 tests for categorical variables, respectively. As urine cotinine level data were non-parametric and contained zero values, they were logarithmically transformed (natural log [x +0.1]). Multivariate logistic regression analyses were subsequently performed to further confirm the association between potential risk factors and HS or occasional snoring respectively. The association was assessed in two logistic regression models: (1) partially adjusted model which was adjusted for age, sex, and BMI z-score; (2) fully adjusted model which was adjusted for age, sex, BMI z-score as well as other factors whose *p* value were<0.1 in partially adjusted model simultaneously. The sleep problems across the snoring frequency groups were compared by χ^2 tests and multiple χ^2 tests with adjusted *p* values (significant at *p*<.016) were used for post hoc pairwise comparisons. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois), and a *p* value <0.05 was considered statistically significant.

2.3 RESULTS

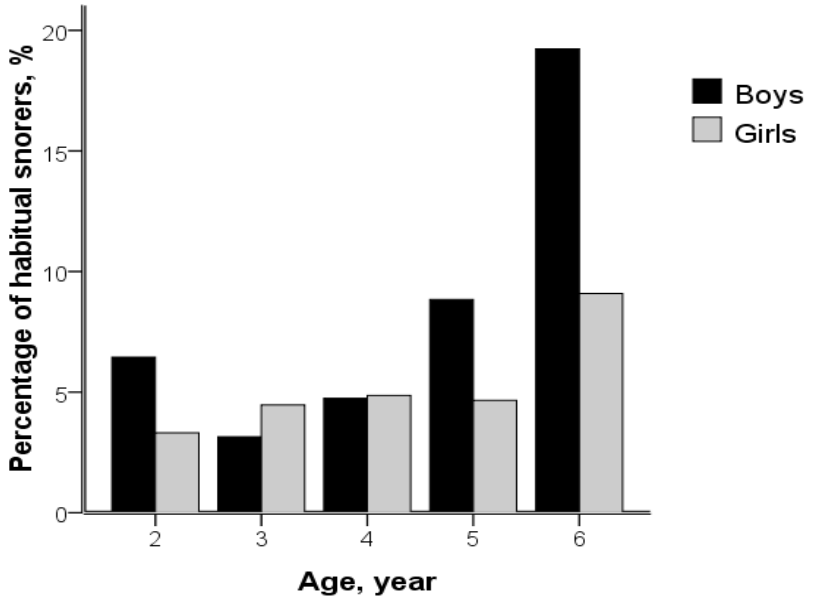
Of 2,954 children enrolled, 2,197 questionnaires were returned giving a response rate of 74.4%. Ten subjects with missing information on snoring were excluded, leaving 2,187 children for final reporting. Of the whole group, 2,085 subjects also completed the ISAAC questionnaire. The age distribution (*p*=0.088), gender (*p*=0.096), snoring frequency (*p*=0.970) and monthly family income (*p*=0.549) did not significantly differ between subjects who completed

the ISAAC questionnaire and those who did not. The characteristics of all the children included in the final analysis are shown in Table 2.2.

2.3.1 *Prevalence of HS*

In total, there were 120 habitual snorers (5.5%, 95%CI 4.5%-6.5%), 974 occasional snorers (44.5%, 95%CI 42.4%-46.6%), and 1,093 non-snorers (50.0%, 95%CI 47.9%-52.1%). Figure 2.1 showed the prevalence of HS by age and sex. Prevalence of HS increased significantly with age (p=0.001) and reached its peak at 6 years of age. Difference in the prevalence of HS between boys (6.2%) and girls (4.7%) did not reach statistical significance in the whole cohort (p=0.131). Neither could significant differences between gender be found in each age subgroup.

Figure 2.1 Prevalence of habitual snoring (HS) by age and gender in preschool children



Age (y)		2	3	4	5	6
Boys	% of HS	6.5	3.2	4.7	8.8	19.2
	Total N	155	349	316	294	52
Girls	% of HS	3.3	4.5	4.9	4.7	9.1
	Total N	151	291	288	236	55
All	% of HS	4.9	3.8	4.8	7.0	14.0
	Total N	306	640	604	530	107

2.3.2 *Risk Factors for HS*

The possible risk factors for HS were compared between different snoring groups (Table 2.2). A number of variables were demonstrated to have a dose-response relationship with snoring frequency. The proportions of older subjects,

boys, household smoking, allergic rhinitis, eczema, food allergy and maternal allergy as well as BMI z-score increased across groups.

Table 2.2 Characteristics of all subjects and distribution of variables according to snoring status in preschool children

	All	Nonsnorers	Occasional snorers	Habitual snorers	*p* for trend
Demographic factors					
Age	4.24 (1.08)	4.19 (1.08)	4.24 (1.06)	4.61 (1.15)	.001
Male gender (%)	53.3	50.3	55.9	60.0	.003
BMI z-score	0.23 (1.07)	0.17 (1.05)	0.28 (1.08)	0.38 (1.22)	.014
Socioeconomic factors					
Monthly family income (%)					.992
<10,000$HK	24.5	25.0	24.6	18.6	
10,000-50,000$HK	69.0	67.6	69.6	77.1	
>50,000$HK	6.5	7.4	5.8	4.2	
Paternal education (%)					.252
Primary school	14.6	15.9	13.7	10.3	
Secondary school	66.9	65.9	66.9	75.0	
Tertiary school	18.5	18.1	19.4	14.7	
Maternal education (%)					.721
Primary school	15.3	16.8	13.9	12.9	
Secondary school	70.1	67.9	71.8	76.7	
Tertiary school	14.6	15.4	14.2	10.3	

(Continued) Characteristics of all subjects and distribution of variables according to snoring status in preschool children

	All	Nonsnorers	Occasional snorers	Habitual snorers	*p* for trend
Envioronmental factors					
Sleep in own room (%)	19.7	19.2	20.6	15.8	.978
Furry pet keeping (%)	6.9	7.0	6.6	8.6	.891
Maternal smoking during pregnancy (%)	3.5	3.0	3.7	6.1	.113
Household smoking					<.001
No smoking (%)	60.6	64.4	56.7	56.9	
1-10 cigarettes/day (%)	32.0	30.0	34.3	31.0	
>10 cigarettes/day (%)	7.5	5.6	9.0	12.1	
ln Urine cotinine/Cr (ng/mgCr)	1.84 (1.11)	1.78 (1.06)	1.92 (1.17)	1.81 (1.01)	.230
Increased urine cotinine (%)	10.8	8.3	13.6	10.8	.081

(Continued) Characteristics of all subjects and distribution of variables according to snoring status in preschool children

	All	Nonsnorers	Occasional snorers	Habitual snorers	*p* for trend
Clinical factors					
Natural birth (%)	65.2	65.5	65.4	60.3	.484
Birth weight <2500g (%)	8.1	8.0	8.4	6.2	.853
Preterm (%)	8.2	8.9	7.7	7.1	.290
Breastfeeding (%)	50.2	50.8	49.9	47.4	.510
Allergic rhinitis (%)	26.6	23.5	27.7	45.7	<.001
Asthma (%)	5.3	5.3	5.1	7.8	.598
Eczema (%)	34.6	32.9	34.6	50.9	.004
Food allergy (%)	3.7	2.7	4.3	6.9	.007
URI during past 4 weeks (%)	31.4	32.7	29.4	35.5	.200
Paternal allergy (%)	34.5	32.8	35.4	42.0	.068
Maternal allergy (%)	33.1	31.9	32.2	50.9	.013

BMI, body mass index; Cr, creatinine; URI, upper respiratory tract infection.

Table 2.3 shows the results of logistic regression analyses identifying risk factors for HS. With reference to the non-snoring group, older age, higher BMI z-score, allergic rhinitis, eczema and maternal allergy were significantly associated with HS in the fully adjusted model.

Table 2.3 Risk factors associated with habitual snorers with reference to non-snorers in preschool children

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Demographic factors						
Age	1.37	<.001	1.2	.016	1.30	.015
	(1.16-1.63)		(1.04-1.50)		(1.05-1.62)	
Male gender	1.48	.045	1.41	.089	1.20	.433
	(1.01-2.17)		(0.95-2.11)		(0.76-1.91)	
BMI z-score	1.21	.040	1.21	.042	1.32	.009
	(1.01-1.45)		(1.01-1.46)		(1.07-1.64)	

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in preschool children

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Socioeconomic factors						
Monthly family income						
10,000-50,000$HK vs	1.38	.193	1.44	.146		
<10,000$HK	(0.85-2.23)		(0.88-2.35)			
>50,000$HK vs <10,000$HK	0.74	.561	0.83	.717		
	(0.27-2.02)		(0.30-2.29)			
Paternal education						
Secondary school vs primary	1.75	.080	1.80	.071	1.40	.389
school	(0.94-3.28)		(0.95-3.40)		(0.65-2.98)	
Tertiary school vs primary school	1.24	.577	1.28	.540	1.14	.782
	(0.58-2.68)		(0.58-2.81)		(0.46-2.84)	
Maternal education						
Secondary school vs primary	1.47	.187	1.43	.224		
school	(0.83-2.60)		(0.80-2.56)			
Tertiary school vs primary school	0.88	.740	0.95	.895		
	(0.40-1.93)		(0.43-2.11)			

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in preschool children

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Envioronmental factors						
Sleep in own room	0.79	.370	0.66	.146		
	(0.47-1.32)		(0.38-1.15)			
Furry pet keeping	1.25	.523	1.35	.403		
	(0.63-2.50)		(0.67-2.72)			
Maternal smoking during	2.09	.088	2.07	.099	1.98	.198
pregnancy	(0.90-4.84		(0.87-4.92)		(0.70-5.63)	
Household smoking						
1-10 cigarettes/day vs no	1.17	.473	1.20	.405	1.39	.198
smoking	(0.76-1.79)		(0.78-1.86)		(0.84-2.28)	
>10 cigarettes/day vs no	2.45	.006	2.09	.029	1.98	.082
smoking	(1.30-4.62)		(1.08-4.07)		(0.92-4.29)	
Urine cotinine/Cr	1.00	.777	1.00	.971		
	(0.98-1.02)		(0.98-1.02)			
Increased urine cotinine	1.35	.598	1.65	.390		
	(0.45-4.05)		(0.53-5.13)			

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in preschool children

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Clinical factors						
Allergic rhinitis	2.74	<.001	2.34	<.001	1.68	.044
	(1.85-4.05)		(1.56-3.52)		(1.01-2.77)	
Asthma	1.51	.274	1.35	.437		
	(0.72-3.13)		(0.64-2.84)			
Eczema	2.12	<.001	2.17	<.001	1.65	.037
	(1.44-3.11)		(1.46-3.23)		(1.03-2.63)	
Food allergy	2.67	.018	2.94	.011	1.44	.505
	(1.19-6.00)		(1.28-6.77)		(0.50-4.25)	
URI during past 4 weeks	1.13	.557	1.33	.187		
	(0.75-1.71)		(0.87-2.04)			
Paternal allergy	1.47	.070	1.68	.019	1.25	.351
	(0.97-2.24)		(1.09-2.59)		(0.78-2.01)	
Maternal allergy	2.22	<.001	2.27	<.001	1.66	.044
	(1.48-3.33)		(1.49-3.44)		(1.01-2.70)	

BMI, body mass index; Cr, creatinine; URI, upper respiratory tract infection.

These analyses were repeated for the less severe categories of snoring. Partially adjusted model showed that male gender (OR 1.25, 95%CI 1.05-1.50, *p*=.015), higher BMI z-score (OR 1.11, 95%CI 1.02-1.21, *p*=.018), food allergy (OR 1.82, 95%CI 1.08-3.06, *p*=.024), household smoking (1-10 cigarettes/day: OR 1.30, 95%CI 1.07-1.59, *p*=.009; >10 cigarettes/day: OR 1.75, 95%CI 1.22-2.52, *p*=.003) and increased urine cotinine (OR 1.85, 95%CI 1.12-3.04, *p*=.016) were significantly associated with presence of occasional snoring. However when fully adjusted, only household smoking (1-10 cigarettes/day: OR 1.37, 95%CI 1.11-1.70, *p*=.003; >10 cigarettes/day: OR 1.65, 95%CI 1.13-2.41, *p*=.010) and increased urine cotinine (OR=1.82, 95%CI 1.08-3.06, *p*=.024) remained statistically significant. As these two variables reflected a similar risk factor and were significantly correlated (*p*<.001), they were entered into the fully adjusted model separately.

2.3.3 Sleep Problems Associated with HS

Habitual snorers were demonstrated to have more problems with going to sleep reluctantly, difficulty in falling asleep, night awakenings and sleep in prone position as well as more overall poor sleep quality than non-snorers (Table 2.4).

Table 2.4 Comparison of sleep problems between snoring status

	Non-snorers	Occasional snorers	Habitual snorers	*p*
Going to bed reluctantly (%)[a,b]	12.6	17.3	24.2	<.001
Difficulty in falling asleep ≥3 nights/week (%)[b]	9.8	12.9	18.3	.006
Night awakenings≥3 nights/week (%)[b,c]	12.4	13.0	25.0	.001
Nocturnal sleep duration<9 hours (%)	2.5	3.2	5.9	.104
Sleep in prone position (%)[b,c]	13.5	13.5	24.4	.004
Overall poor sleep quality (%)[b,c]	4.5	6.2	17.5	<.001

[a] $p<.016$, non-snorers vs occasional snorers.
[b] $p<.016$, non-snorers vs habitual snorers.
[c] $p<.016$, occasional snorers vs habitual snorers.

2.4 DISCUSSIONS

To our knowledge, this is the first population-based study carried out in this region to examine the prevalence of HS among Chinese 2- to-6-year-old preschool children. It was a territory wide survey with random clustering, therefore a reliable representative of the whole of Hong Kong. The prevalence rate of HS was 5.5% in this age group. Older age, higher BMI z-score, allergic rhinitis, eczema and maternal allergy were identified to be independent risk factors associated with HS. Habitual snorers also had problems with initiating and maintaining sleep and they were more likely to adopt unusual sleep posture.

Our prevalence of HS in preschool children is lower than figures from Italy,[46] the United States,[25, 47] Australia,[49] Britain[50] and Turkey[44] where rates from 7.6% to 34.5% had been reported. Our finding of 5.5% was consistent with figures reported from Singapore (6.0%)[54] (Table 2.1). Such a wide discrepancy may be attributed to different races, environment, definition of HS and methods of sampling. It may be because Chinese children accounted for over 70% of their population that the Singapore's study[54] provided a similar prevalence rate as ours. Moreover HS was demonstrated to be less prevalent in Chinese children than that in Malay children in that survey. [54] In a recent multi-centre survey conducted across Asia Pacific in children aged from birth to 36 months, Chinese children had a lower prevalence of HS than Caucasian children.[51] It is likely that inter-ethnic differences may be present in craniofacial morphology, body fat distribution and neural control of the upper airway muscle interact to produce the snoring susceptible phenotype.

In our study, older age increased the risk of having HS and the prevalence rate peaked at 6 years of age. Our previous prevalence study conducted in primary school Hong Kong children and other researchers also documented that HS was more prevalent at 6 or 7 years of age.[26, 28, 60, 69, 71] This association between age and HS seems to be in accordance with the peak age of tonsillar hypertrophy.[195] Adenotonsillar hypertrophy which is a well-known cause of upper airway obstruction has been identified as a risk factor for HS in children.[48, 60, 64, 68]

It is underastandable that higher BMI z-score was found to be a significant independent risk factor associated with snoring. Obesity leads to restricted upper airway size primarily through overgrowth and crowding of soft tissues and has been regarded as a well-documented risk factor for childhood obstructive sleep apnoea (OSA).[15] MRI data in adults showed that volumes of soft tissue (tongue, lateral pharyngeal walls, parapharyngeal fat pads, total soft tissue) increased significantly with increasing BMI.[196] Our research group also demonstrated that obesity was correlated with enlarged adenoids and smaller velopharyngeal isthmus in children and was a risk factor for obstructive SDB.[197] In primary school children, increasing epidemiology studies have also identified higher BMI z-score as an independently risk factor for HS.[26, 28, 60, 66, 83, 85] Although adenotonsillectomy is still the first-line therapy for childhood OSA, its cure rate in obese children is unsatisfactory.[96] Thereby weight reduction must be a necessary component in the management of obesity-related snoring or OSA.

Our result indicated that allergic rhinitis, eczema and maternal allergy were risk factors associated with HS. Atopic diseases such as allergic rhinitis, asthma and eczema as independent risk factors for HS have been previously reported.[26, 28, 43, 48-50, 54, 58, 60, 62, 65, 68, 69, 71, 83, 85, 88, 198] Allergic rhinitis related inflammation and narrowing to the upper airways would increase flow resistance and hence one's liability to snore. Positive parental allergy affects offsprings' HS may be through familial transmission of allergic nature [199] or snoring itself, as allergy is also associated with snoring in adults.[200] At present

several research studies have revealed parental snoring as a significant risk factor for their children's HS.[26, 43, 60, 62, 88] There seemed to be a stronger maternal association in our study. It could not simply be explained by the traditional caretaking role of mothers in Hong Kong Chinese families. Alternative reasons for the maternal predisposition of snoring such as genetic component via maternal transmission or other hidden confounding factors would need further study. Intranasal steroids may ameliorate mild childhood OSA,[96] while studies on whether snoring without apnoea could also be relieved by anti-inflammatory threatment are still lacking and worth elaborating.

Controversial findings exist in terms of the role of ETS exposure in developing HS.[26, 28, 43, 46, 48, 50, 54, 58, 60, 63, 65, 66, 68, 71, 198] To our knowledge, this is the first population-based study using urinary cotinine together with questionnaires to examine the effect of ETS on snoring in children. Interestingly our findings indicated that occasional snoring seemed to be more significantly associated with passive smoking than habitual snoring did, measured by urine cotinine. In this study, the HS group included greater proportion of children with atopic diseases and parental allergy (Table 2), thus parents from this group are more likely to avoid smoking in close proximity for the sake of their children's or their own health, resulting in a lower urinary cotinine concentration than expected. In addition, the sample size of subjects who underwent urine cotinine test was 349, 309 and 36 in nonsnorers, occasional snorers and habitual snorers respectively. The small sample size of HS group could explain the negative results. Overall we still provided evidence suggesting exposure to ETS

as a highly possible independent risk factor for snoring in preschoolers. One study conducted in adults suggested that smoking may induce oropharyngeal narrowing and collapse through histological changes of the uvular mucosa due to increased neurogenic inflammation.[201] Further intervention study involving smoking cessation is required to confirm this finding. In addition, effects of general air pollution on childhood snoring would be interesting and potentially significant.

HS was shown to be linked with bedtime resistance, difficulty falling asleep, increased night awakenings and sleep in prone position, and overall sleep quality was reduced compared to nonsnorers. These findings are in agreement with a number of previous results in preschool children.[43, 45, 54, 57] Recurrent snoring may signify partial obstruction of upper airway and children would choose prone position to achieve better upper airway patency. Hypoxia during sleep would be compensated by arousals or even awakenings to resume normal neuromuscular regulation to maintain upper airway patency. Hence disturbed sleep could lead to sleep resistance in preschool children.

One limitation of our study was the lack of objective measurements for snoring, a limitation shared with other community-based surveys. But the majority of our subjects shared bedrooms with their parents who might pay more attention to their children's sleep behaviour at this age. A previous publication showed a significant and independent association between parentally reported and objectively measured HS.[46] Because of restricted resources, overnight monitoring recording snoring and other sleep-related

parameters was clearly impractical for a large population survey. Another limitation was that we asked parents about their children's snoring during the past two weeks and the questionnaires were distributed altogether during one summer. Therefore seasonality of symptoms was not dealt with adequately, as presence of snoring might be affected by seasonal variation of allergic diseases.

In conclusion, we found the prevalence of HS in Chinese preschool children to be lower than counterparts in other countries. Older age, BMI z-score, allergic rhinitis, eczema and maternal allergy were independent risk factors of HS. Exposure to ETS was an independent risk factor of occasional snoring. HS was also demonstrated to be associated with various sleep disturbances.

CHAPTER 3

Prevalence of Snoring in Chinese School-aged Children and Adolescents

3.1 INTRODUCTION

Snoring is a low-frequency sound produced by vibrations of the soft tissues in the oropharynx during sleep.[189] It is the most common manifestation of sleep-disordered breathing (SDB), with severity ranging from primary snoring to obstructive sleep apnoea (OSA).[90] In children, habitual snoring (HS) has been demonstrated to be associated with a variety of clinical sequelae even in the absence of sleep apnoea or hypopnoea, including impaired neurobehavior, poor academic performance,[31, 37, 186] elevated blood pressure,[175] and reduced endothelial function.[174]

Various research groups have investigated prevalence of HS in school-aged children and adolescents but have yielded heterogeneous results (Table 3.1). In Hong Kong, a telephone survey was carried out involving primary school children and the prevalence of HS was reported to be 10.9%. However, the study had a response rate of only 50%, such that sampling bias might exist.[62] Our research group utilized a validated parent-completed questionnaire to conduct a territory-wide survey in children aged 6-13 years in 2003, giving a HS prevalence rate of 7.2%.[26] To our knowledge, population-based prevalence of HS in secondary school adolescents in this locality is not available.

A variety of risk factors have been reported to associate with HS in children and adolescents. Several studies demonstrated a positive relationship between HS and male gender, obesity, allergic rhinitis (AR), asthma, exposure to tobacco smoke and low socioeconomic status, however these positive associations were not consistent across all studies (Table 3.1).

In this study, we aimed to determine the prevalence of HS and its associated risk factors in children and adolescents aged 8-17 years in Hong Kong, using a population-based approach.

Table 3.1 Published community-based studies on prevalence and risk factors of HS in school-aged children and adolescents

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
Frequently or almost everyday	1,164	Turkey[28]	7yr-13yr	3.5	Younger age	Male	+	+			+	+		-
Frequently or almost always	20,152	China[60]	5yr-12yr	12.0	Peak age 7yr	Male	+	+	+			+		+
Yes/No	652	Belgium[61]	6yr-12yr	32.6				+	+*					
>=3 nights/wk	6,349	Hong Kong[26]	5yr-14yr	7.2	Peak age 6yr-7yr	Male	+	+	+	-	+	-		-
>=6 nights/wk	3,047	Hong Kong[62]	6yr-12yr	10.9		Male		+						
Often or always	2,147	Turkey[63]	5yr-13yr	7.0	Peak age 11yr-13yr	Male			+		+	+		
Everyday	1,211	Turke[64]	6yr-13yr	2.4										
Always or often	806	US[65]	6yr-12yr	15.1	-	Male		+						
Frequently or always	1,129	Germany [66]	9.6±0.7 yr	10.0	-	-	+				-	-		+

(Continued) Published community-based studies on prevalence and risk factors of HS in school-aged children and adolescents

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
Yes/No	1,404	Sweden[67]	6yr-11yr	23.0										
Most nights	1,008	Thailand [68]	6yr-13yr	8.5	-	-	-	+				-		
Often	1,615	Italy [69]	6yr-13yr	7.3	Younger age	-		+	-			+		
Frequently	976	Portugal [70]	6yr-11yr	8.6	-	-					+			
>=4 nights/wk	996	Australia [71]	4yr-12yr	15.2	Younger age	-		+	+			+		
Frequently	998	Brazil [72]	9yr-14yr	27.6								+		
Frequently	5,979	China[73]	2yr-12yr	5.6	-	Male								
At least some nights	473	US[74]	3yr-14yr	22.9	Peak age 3yr-6yr		-	+	-					
>3 nights/wk	1,198	Turkey[75]	3yr-11yr	3.3		-		+	-			+		
Always	895	Italy[76]	3yr-11yr	4.9		Male								

(Continued) Published community-based studies on prevalence and risk factors of HS in school-aged children and adolescents

Definition of habitual snoring	N	Location	Age range	Prevalence, %	Risk factors of habitual snoring									
					Age	Gender	Obesity	AR	Asthma	Eczema	URI	Passive smoking	Race	Low SES
Yes/No	909	Nigeria [77]	3yr-16yr	34.2	Peak age 3yr-6yr	-								-
Always	3,680	Greece [78]	1yr-18yr	4.2	-	Male		+				+		
Frequently or almost always	1,481	US[81]	4yr-11yr	10.5	-	-							Hispanic	
Often	1,784	Turkey [12]	4yr-17yr	4.1										+
Often	2,209	Italy[83]	10yr-15yr	5.6	Older age	Male	+	+	-			+		+
Every or nearly every night	1,014	US[84]	13yr-16yr	6										
>=3 nights/wk	3,871	Korea[27]	15yr-18yr	11.2		-	+					+		
Often or always	1,030	Turkey [85]	12yr-17yr	4.0	Younger age	-	+	+				+		
Very often	332	Austria [86]	11yr-15yr	2.1										
Often or every night	24,682	France [87]	15yr-20yr	4.8	-	Male	+					+**		
>=3 nights/wk	2,900	Iran[88]	11yr-17yr	7.9		Male			+					

HS, habitual snoring; AR, allergic rhinitis; URI, upper respiratory tract infection; SES, socio-economic status.
*wheezing; **active smoking

3.2 METHODS

3.2.1 Study Population

This prevalence study of HS in school-aged subjects was carried out concurrently with a community-based study aiming to develop 24-hour ambulatory blood pressure reference values for Hong Kong Chinese children and adolescents aged 8-17 years. Healthy Chinese primary school children and secondary school adolescents who are Hong Kong permanent residents were eligible for inclusion. Subjects were excluded from the study if they were reported by their parents to have cardiovascular, renal or neuromuscular diseases or chromosomal abnormalities, or if they had previously undergone upper airway surgery.

Based on our previous study carried out in primary school children, 7.2% of children had HS.[26] Assuming the prevalence of HS was also the same for secondary school adolescents and a maximum error of estimate of 2%, the estimated sample size with 95% confidence needed for a population prevalence was 642 children.[191]

A two-stage cluster sampling method was used. With the assistance of the Department of Education, a sampling frame of all primary and secondary schools in Hong Kong was complied. The first stage involved selection of schools and the second stage the students. All students who joined the study were randomly selected by computer generated numbers. Consequently a total of 14 primary schools and 18 secondary schools participated. In total, 1,615 children and adolescents were given sleep symptom questionnaires to be

completed by their parents/care-givers (see the section of ‘Questionnaires’). Informed written consent was obtained from the subjects’ parents. Approval by the ethics committee of the Chinese University of Hong Kong was also obtained.

3.2.2 Questionnaires

The parents of all participants were invited to complete a questionnaire providing demographic information, sleep symptom / pattern and family or personal medical history (Appendix 3) Snoring frequency was assessed by a single question, namely “How often did he/she snore during sleep over the past one year?” and was rated on a 4-point scale: 1=never; 2=less than one night per month; 3=one to two nights per week; 4=three nights or more per week. The subjects were divided into three groups according to snoring frequency for comparisons: (1) non-snorers, those scoring “1”; (2) occasional snorers, those scoring “2” or “3”; and (3) habitual snorer, those scoring “4”. A simplified Chinese version of modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was also completed by parents (Appendix 4).

3.2.3 Anthropometry Assessment

A team of three trained research staff visited each selected school on a pre-arranged date to collect the anthropometric data. All instruments were validated following the standard methods recommended by the manufacturers, and the balances were zero calibrated. Standing height without shoes was measured using a height measuring instrument (seca 217, UK) to the nearest

0.1 cm. Body weight was measured with the lightest clothing to the nearest 0.1 kg by an electronic weighing scale (Tanita BF-522, Japan). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and were converted to z-scores appropriate for age and gender, according to local reference.[193] All participants completed a validated self-reported Pubertal Development Scale in Chinese version for pubertal staging.[202] Subjects were categorized as prepubertal, defined as Tanner stage 1, or pubertal, defined as Tanner stage 2 or greater.

3.2.4 Statistical Analyses

Data were presented as mean (standard deviation) and percentages for continuous and categorical data, respectively. The prevalence of HS, occasional snoring and non-snoring and their 95% confidence interval (CI) were calculated.[191] The trends of characteristics across snoring frequency groups were analysed using analysis of variance (ANOVA) tests for continuous variables and linear-by-linear association χ^2 tests for categorical variables, respectively. Multivariate logistic regression analyses were subsequently performed to further confirm the association between potential risk factors and HS or occasional snoring respectively. The association was assessed in two logistic regression models: (1) partially adjusted model which was adjusted for age, sex, and BMI z-score; (2) fully adjusted model which was adjusted for age, sex, BMI z-score as well as other factors whose *p* value were<0.1 in partially adjusted model simultaneously. All statistical analyses were performed using

SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois), and a *p* value <0.05 was considered statistically significant.

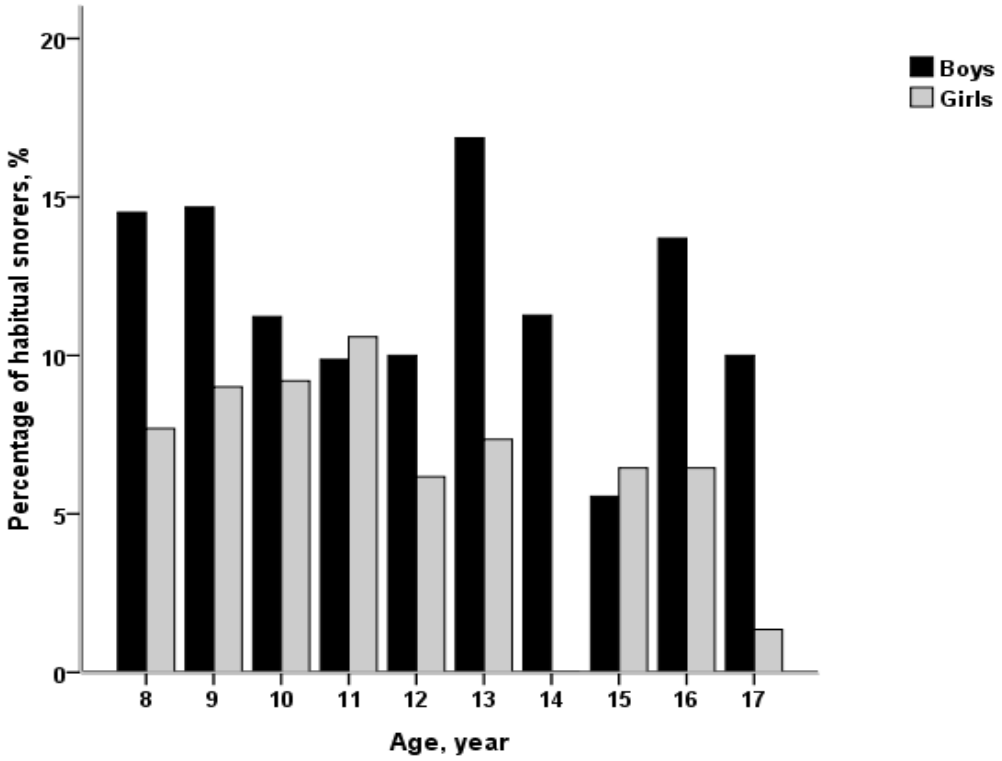
3.3 RESULTS

All of the 1,615 subjects returned both questionnaires. Two subjects with missing information on snoring frequency were excluded, leaving 1,613 completed questionnaires for final analysis. The characteristics of all subjects are shown in Table 3.2.

3.3.1 Prevalence of HS

A total of 149 subjects had HS (9.2%, 95%CI 7.8%-10.6%) and 546 had occasional snoring (33.8%, 95%CI 31.5%-36.1%). Figure 3.1 showed the prevalence of HS by age and gender. No significant differences in prevalence of HS were found between age groups either for the cohort as a whole or exclusively for boys or girls. While linear-by-linear association χ^2 test showed that there was a significant decreasing trend with increasing age in the prevalence of HS in the whole population (*p*=.021) and in girls (*p*=.016). In general boys had significantly higher prevalence of HS than girls (11.9% vs 6.6%, *p*<.001).

Figure 3.1 Prevalence of habitual snoring (HS) by age and gender in school-aged children and adolescents



Age (y)		8	9	10	11	12	13	14	15	16	17
Boys	% of HS	14.5	14.7	11.2	9.9	10.0	16.9	11.3	5.6	13.7	10.0
	Total N	62	109	98	81	100	83	71	72	73	60
Girls	% of HS	7.7	9.0	9.2	10.6	6.2	7.4	0	6.5	6.5	1.4
	Total N	65	111	87	85	81	68	78	62	93	74
All	% of HS	11.0	11.8	10.3	10.2	8.3	12.6	5.4	6.0	9.6	5.2
	Total N	127	220	185	166	181	151	149	134	166	134

3.3.2 Risk Factor for HS

The possible risk factors for HS were compared between different snoring groups (Table 3.2). BMI z-score and the proportions of boys, higher parental education, AR, eczema, food allergy and parental allergy increased whereas age decreased across different snoring frequency groups, from non-snoring to habitual snoring.

Table 3.2 Characteristics of all subjects and distribution of variables according to snoring status in school-aged children and adolescents

	All	Non-snoring	Occasional snoring	Habitual snoring	*p* for trend
Demographic factors					
Age (year)	12.8 (2.8)	13.1 (2.8)	12.3 (2.8)	12.3 (2.7)	<.001
Male gender (%)	50.2	44.8	55.3	64.4	<.001
BMI z-score	0.33 (1.04)	0.20 (1.00)	0.39 (1.05)	0.87 (1.12)	<.001
Puberty (%)	86.2	87.8	83.5	86.6	.131
Socioeconomic factors					
Patermal education (%)					.009
Primary school	13.7	15.3	11.9	11.4	
Secondary school	67.4	67.2	69.6	62.4	
Tertiary school	18.6	17.5	18.5	26.2	
Maternal education (%)					.009
Primary school	13.3	15.4	10.4	11.4	
Secondary school	73.5	72.3	76.7	70.5	
Tertiary school	13.0	12.3	12.8	18.1	

(Continued) Characteristics of all subjects and distribution of variables according to snoring status in school-aged children and adolescents

	All	Non-snoring	Occasional snoring	Habitual snoring	*p* for trend
Environmental factors					
Household pet (%)	20.0	21.7	18.1	16.8	.056
Household smoking (%)					.093
Nil	69.0	70.4	67.9	64.4	
1-10 cigarettes/day	23.5	22.2	26.0	22.8	
>10 cigarettes/day	7.5	7.4	6.0	12.8	
Clinical factors					
Birthweight <2500g (%)	6.2	6.3	6.2	6.1	.937
Preterm (%)	5.7	5.0	6.2	8.1	.113
Breastfeeding (%)	50.3	49.2	52.9	47.7	.630
Asthma (%)	6.0	5.6	6.0	8.7	.190
Eczema (%)	11.6	10.4	12.6	16.1	.029
Allergic rhinitis (%)	26.6	21.0	33.0	38.3	<.001
Food allergy (%)	8.7	6.6	11.5	11.4	.002
Paternal allergy (%)	22.9	18.4	28.2	31.5	<.001
Maternal allergy (%)	25.2	20.9	31.3	29.5	<.001

Table 3.3 shows the results of logistic regression analyses identifying risk factors for HS. With reference to the non-snoring group, male gender, higher BMI z-score, more household smoking, presence of AR and paternal allergy were significantly associated with HS in the fully adjusted model

Table 3.3 Risk factors associated with habitual snorers with reference to non-snorers in school-aged children and adolescents

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Demographic factors						
Age	0.89	.001	0.93	.030	0.95	.154
	(0.84-0.95)		(0.87-0.99)		(0.88-1.02)	
Male gender	2.23	<.001	2.08	<.001	2.00	<.001
	(1.56-3.20)		(1.43-3.01)		(1.36-2.94)	
BMI z-score	1.96	<.001	1.85	<.001	1.97	<.001
	(1.63-2.36)		(1.53-2.23)		(1.61-2.40)	
Puberty	0.90	.678	0.93	.815		
	(0.54-1.50)		(0.52-1.67)			

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in school-aged children and adolescents

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Socioeconomic factors						
Paternal education						
Secondary school vs primary school	1.25 (0.72-2.16)	.413	1.21 (0.69-2.13)	.513	1.06 (0.56-2.02)	.851
Tertiary school vs primary school	2.01 (1.09-3.71)	.026	1.86 (0.98-3.53)	.057	1.46 (0.65-3.27)	.355
Maternal education						
Secondary school vs primary school	1.31 (0.76-2.26)	.326	1.30 (0.74-2.28)	.364	1.04 (0.54-1.99)	.907
Tertiary school vs primary school	1.98 (1.03-3.82)	.041	1.87 (0.95-3.71)	.072	1.27 (0.52-3.08)	.603

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in school-aged children and adolescents

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Envioronmental factors						
Pet keeping	0.73 (0.46-1.15)	.171	0.83 (0.52-1.34)	.447		
Household smoking						
1-10 cigarettes/day vs no smoking	1.12 (0.74-1.71)	.594	0.93 (0.60-1.45)	.744	1.22 (0.76-1.95)	.404
>10 cigarettes/day vs no smoking	1.88 (1.08-3.27)	.025	1.93 (1.08-3.47)	.028	2.34 (1.26-4.34)	.007

(Continued) Risk factors associated with habitual snorers with reference to non-snorers in school-aged children and adolescents

	Univariate model		Partially adjusted model		Fully adjusted model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Clinical factors						
Allergic rhinitis	2.33 (1.61-3.36)	<.001	2.45 (1.66-3.61)	<.001	2.07 (1.37-3.13)	.001
Asthma	1.63 (0.86-3.07)	.134	1.31 (0.67-2.58)	.428		
Eczema	1.66 (1.02-2.70)	.041	1.73 (1.04-2.88)	.036	1.20 (0.69-2.10)	.515
Food allergy	1.81 (1.03-3.19)	.041	1.93 (1.06-3.53)	.031	1.57 (0.82-2.99)	.170
Paternal allergy	2.04 (1.39-2.99)	<.001	2.11 (1.41-3.15)	<.001	1.61 (1.04-2.51)	.033
Maternal allergy	1.59 (1.08-2.33)	.020	1.63 (1.08-2.45)	.019	1.25 (0.81-1.93)	.322

These analyses were repeated for occasional snoring. Fully adjusted model showed that younger age (OR 0.91, 95%CI 0.88-0.95, *p*<.001), male gender (OR 1.48, 95%CI 1.20-1.85, *p*<.001), higher BMI z-score (OR 1.20, 95%CI 1.08-1.34, *p*<.001), paternal allergy (OR 1.40, 95%CI 1.07-1.82, *p*=.015), maternal allergy (OR 1.43, 95%CI 1.10-1.85, *p*=.007), food allergy (OR 1.72, 95%CI 1.17-2.53, *p*=.006) and AR (OR 1.51, 95%CI 1.17-1.96, *p*=.002) were significantly associated with presence of occasional snoring.

3.4 DISCUSSIONS

To our knowledge, this is the first epidemiological study to determine the prevalence of HS and its related risk factors covering both primary and secondary school subjects in Hong Kong. Our findings showed that the overall prevalence of HS was 9.2% in 8 to 17-year old children / adolescents, and the probability of having HS increased with younger age, male gender, obesity, atopy, parental allergy and exposure to household smoking after full adjustment.

The prevalence of HS in school-aged children and adolescents from different countries or areas vary widely (Table 3.1). Such a wide discrepancy may be attributed to different age groups, races, environment, definition of HS and methods of sampling. Our prevalence seemed to be at the average level amongst the prevalence rates reported worldwide. In terms of prevalence of HS in primary school children aged 8-11 years in this study, our findings were comparable to previous data from Germany,[34] Thailand,[68] Portugal,[70] Italy[69] as well as China[60] and another local study[62] but lower than figures reported

from Belgium,[61] Brazil[72] and Sweden[67] and higher than the prevalence rate in Turkey.[28, 64] In 2003, our research group conducted a population-based survey in children aged 6-13 years using identical definition of HS and generated a prevalence rate of 7.2%,[26] which was a little lower than what we derived at present in 2012. It is possible that there is increasing prevalence of HS amongst primary school children in Hong Kong over the past decade, parallel to a concurrent increase trend in the prevalence of childhood obesity.[203, 204]

The majority of studies examining prevalence of HS in adolescents aged 12-17 years reported a rate <10%,[27, 83-88] seemingly lower than the rate reported for primary school children (Table 3.1). In our study we also demonstrated that older subjects were less likely to have HS than younger ones, especially in girls. It may be explained by the fact that enlarged tonsils which is a well-known risk factor for upper airway obstruction reduce in size with age.[205] However the prevalence of habitual snoring in our school-aged children and adolescents were higher than that in our preschool children (Chapter 2). It may be attributed to the higher average BMI z-score in the older population compared to the younger preschoolers.

Unlike preschool children, significant difference in prevalence of both HS and occasional snoring between genders was found in children aged 8-17 years. Male gender was also demonstrated to be a significant risk factor for HS by a number of other research (Table 3.1). Whether hormonal factors come into play in this phenomenon needs further investigation. Adult studies showed that oestrogen was protective against upper airway collapse,[206] and there were

studies conducted in men suggesting that testosterone could induce or exacerbate OSA.[207, 208] This may explain our results as >85% of the subjects entered pubertal stage during which the sex hormones undergo remarkable changes. Such hormonal changes may also be the reason why we found that boys did not follow the trend of having a lesser chance of developing HS with increasing age. However the mechanism of gender effects on SDB in children is still poorly defined, and future studies in this area is needed.

Higher BMI z-score was found to be a significant independent risk factor associated with snoring, which was consistent with several previous research studies (Table 3.1). In our study, BMI z-core decreased with increase in age ($r=-0.124$, $p<.001$), so it might explain why there was a significant decreasing trend with increasing age in the prevalence of HS. It is understandable because obesity leads to restricted upper airway size primarily through overgrowth and crowding of soft tissues and has been regarded as a well-documented risk factor for childhood OSA.[15] MRI data in adults showed that volumes of soft tissue (tongue, lateral pharyngeal walls, parapharyngeal fat pads, total soft tissue) increased significantly with increasing BMI.[196] Our research group also demonstrated that obesity correlated with enlarged adenoids and smaller velopharyngeal isthmus in children and was an important risk factor for obstructive SDB.[197] Although adenotonsillectomy is still the first-line therapy for childhood OSA, residual disease was as high as 73% in obese children.[96] Therefore weight reduction should be a necessary component in the management of obesity-related snoring or OSA.

Our result indicated that allergic rhinitis, food allergy, eczema as well as paternal and maternal allergy were risk factors associated with HS and/or occasional snoring. Atopic diseases such as allergic rhinitis, asthma and eczema as independent risk factors for HS have been reported before (Table 3.1). Allergic rhinitis related inflammation and narrowing to the upper airways would increase flow resistance and hence one's liability to snore. Positive parental allergy affects offsprings' HS may be through familial transmission of allergic nature[199] or snoring itself, as allergy is also associated with snoring in adults.[200] Several research studies have revealed parental snoring as a significant risk factor for their children's HS (Table 3.1). Intranasal steroids may ameliorate mild childhood OSA,[96] while studies on whether snoring without apnoea could also be relieved by anti-inflammatory treatment are still lacking and worth exploring.

In addition, we found that more than 10 cigarettes smoked daily by family members was positively associated with HS, a finding consistent with what has been reported previously (Table 3.1). We suggested that when a child's exposure to environmental tobacco smoke (ETS) reached a certain threshold, its adverse impact on inducing development of snoring would occur. The mechanism whereby ETS exposure leads to snoring remains unclear. One study conducted in adults suggested that smoking may induce oropharyngeal narrowing and collapse through histological changes of the uvular mucosa due to increased neurogenic inflammation.[201] Clinicians have always been focusing the treatment for childhood SDB on surgery or medication. Our findings

suggested that environmental factors such as ETS should also be paid attention to in the management of childhood SDB. Parental smoking cessation might be important in reducing children's snoring problem.

Lack of objective measurements for snoring was an important draw-back in this study. It was also a limitation shared by many other community-based surveys. Majority of our subjects co-roomed with their parents, so reported snoring frequency should be relatively reliable. Furthermore a recent publication on preschool children showed a correlation between parentally reported and objectively measured HS.[46] As a result of limited resources, overnight monitoring for snoring and other sleep-related parameters was not possible for such a large-scale population study. Another limitation was the lack of a pilot study to calculate the sample size we needed for this population-based survey. We assumed that the prevalence rate in secondary school adolescents was the same as that in primary school children. While the actual rate was lower for older subjects, thus our assumed sample size would have been adequate.

In conclusion, we found the prevalence of HS in Chinese school-aged children and adolescents was comparable to figures reported from other countries. Younger age, higher BMI z-score, atopy, parental allergy and passive smoking were independent risk factors.

CHAPTER 4

Neurocognitive Functions in School-aged Children with Primary Snoring

4.1 INTRODUCTION

Snoring is the most common symptom of pediatric sleep-disordered breathing (SDB), which includes a spectrum of diseases with severity ranging from primary snoring (PS) to obstructive sleep apnea (OSA).[90, 91] Snoring is an upper airway breathing sound or noise caused by vibrations of the pharyngeal tissues during sleep, and partial or complete occlusion of the upper airway is a necessary requirement for occurrence of snoring. [1] It has been shown that children with reported by their parents to have snoring were at higher risk of having neurobehavioral problems than non-snoring subjects, including poor academic performance,[25, 28-31] hyperactivity,[28, 32, 33] inattention,[32, 34] daytime sleepiness,[25, 34, 35] anxious/depressed mood,[36] emotional reactivity problems,[34, 36] and intelligence deficits.[37] However these studies did not perform polysomnography (PSG) to ascertain whether OSA was present.

In terms of the existing studies which involved PSG, there is increasing evidence to suggest that children with OSA have deficits in a number of neurocognitive domains resulting from intermittent hypoxia and sleep fragmentation, including attention,[209, 210] intelligence,[105, 211] executive function,[97, 105, 212, 213] memory and learning skills,[101, 104-107] and school performance.[211, 214, 215] In contrast, studies investigating whether PS, defined as snoring without apnoea or hypopnoea[170] is also related to neurocognitive

problems are scarce. A few studies demonstrated that even PS might also exhibit neurobehavioral impairments.[106, 180, 183, 185, 186] However such positive results are not consistently found in other studies.[97, 182]

Previous studies were also limited in their study design. Majority have recruited only hospital attendants, and often neurocognitive assessment was not based on objective assessment tools carried out by qualified clinical psychologist. Therefore in this study, we aimed to examine the neurocognitive functioning in school-aged children with PS, by using a community-based sample and a battery of objective measures of intelligence, memory, learning and attention. We hypothesized that children with PS had poorer neurocognitive functioning than non-snoring controls.

4.2 METHODS

4.2.1 Subjects and Study Design

Between July 2000 and December 2001, our group established a cohort of 1,057 mother-infant pairs by recruiting mothers and their off-springs from consecutive deliveries at the Prince of Wales Hospital, Hong Kong.[216] We wanted to study the prenatal exposure to methylmercury in newborn infants in Hong Kong and its neurotoxic effects. In the original study, mothers who delivered term babies were recruited if consent was obtained. Between June 2007 and June 2010, children in this cohort were invited to participate in a follow-up neurocognitive function study. Parents were asked to complete two sets of questionnaires. The child was excluded if he or she suffered from a

condition which was associated with adverse neurodevelopmental outcome, but known to be unrelated to Hg exposure, for example, birth asphyxia, severe head injuries, syndromal disorders and neurodegenerative conditions secondary to metabolic or genetic diseases. Children who had periodic limb movements (PLMS)[222] in sleep determined by PSG were also excluded. This study was approved by the Ethics Committee on Clinical Research of the Chinese University of Hong Kong.

4.2.2 Questionnaires

Two self-designed parent-reported questionnaires that aimed to capture the children's sleep problems, parental occupation and education level and family income were completed (Appendix 5 and Appendix 6). The question on snoring was "Does your child snore when he/she is asleep?" and the options given were "Yes" and "No". The socio-economic status of parents was assessed based on the self-coded National Statistics Socio-Economic Classification (NS-SEC) of the Office of National Statistics of the United Kingdom (http://www.ons.gov.uk/about-statistics/classifications/current/ns-sec/self-coded/index.html).

4.2.3 Anthropometry Measurements

Body weight and standing height were measured with a calibrated weighing scale and stadiometer, respectively. BMI was calculated as

weight/height^2 (kg/m^2) and was translated to BMI z-score according to the local reference data.[193]

4.2.4 Neurocognitive Measurements

Children were assessed in a one-to-one interview by a qualified clinical psychologist in a dedicated assessment room, and the following neurocognitive measurements were carried out according to standardized protocols.

4.2.4.1. Hong Kong-Wechsler Intelligence Scale for Children

Hong Kong-Wechsler Intelligence Scale for Children (HK-WISC) contained a panel of psychological sub-tests, not requiring reading or writing, to measure children's intelligence with standardized procedures and have been validated locally for children from 5 to 15 years old.[217] HK-WISC consists of two parts: the Verbal Scale and the Performance Scale. Scoring was done by HK-WISC criteria.

The Verbal Scale related to children's verbal concept formation and verbal expression. Three sub-tests were included:

(1) Information – general knowledge questions would be asked to assess the child's understanding of factual knowledge;

(2) Similarities – the child would be asked to categorize two items/concepts to measure the ability of abstract reasoning;

(3) Vocabulary – the child would be required to explain the meanings of different vocabularies in order to review their language development and word knowledge.

The Performance Scale consisted of two subtests:

(1) Picture Arrangement – the child would be asked to sequence cartoon pictures to form a sensible story, thus testing child's planning ability;

(2) Block Design – the child would be asked to position blocks according to a pattern of a displayed model so as to measure the child's spatial analysis.

The HK-WISC Short Form was used in our study.[218, 219] The selection of the combination of the final tetrad to make up the Short Form took into consideration the potential of yielding most clinical information and high validity coefficients. Two subtests were selected from each of both the Verbal and Performance Scales. For children aged from 5 to 8, subtests Similarities, Information, Picture Arrangement and Block Design were given. For children aged 9 to 11, the subtests were similar to previous combination with Information replaced by Vocabulary. Scaled scores of the sub-tests were calculated for these two scales and a total IQ score was generated. Higher total IQ score implied that the child had a higher general intelligence.

4.2.4.2. Hong Kong List Learning Test

The Hong Kong List Learning Test (HKLLT) is a Chinese language based list-learning test to assess children's verbal memory and learning abilities.[220] It contains a 16-word list comprising two-character that are nouns in four different

categories. The words were spoken out by the psychologist while the children were required to memorize and recall as many words as they could immediately. After three of the above learning trials (trial 1-3), there were two delayed trials, one after 10 minutes (trial 4) and then another after 20 minutes (trial 5). Children were required to recall the words without being prompted by the psychologist. Randomly-presented word-list (Random condition) was chosen. Reported words not on the word list and repetition of any words in trial 3 were regarded as intrusion error and perseveration error, respectively. The parameter “Learning” was calculated by summing the score of trials 1 to 3. For short and long delay recall difference, results were calculated from the differences between trials 4 and 5 to trial 3, respectively (*i.e.*, trial 4 or 5 – trial 3). In this test, the more words they could remember the better the performance in verbal memory and learning. The larger the difference in the delayed recall trials the poorer retention ability.

4.2.4.3 Test of Everyday Attention for Children (TEA-Ch)

Test of Everyday Attention for Children (TEA-Ch) is a standardized and normed clinical battery for children for assessment across different attentional capacities.[221] The sub-tests Sky Search and Map Mission were selected to measure selective attention. Moreover, the sub-tests Sky Search DT and Walk, Don’t Walk were chosen to assess the capacity of sustained attention. In each sub-test, scaled scores were calculated and higher score indicated better performance in the corresponding attention capacity.

Sky search is a brief, timed subtest. Children need to find as many target items (pairs of identical spacecrafts) as possible on a sheet with very similar distracter spacecrafts. In the second part no distracters are present. Time taken and number of correct targets are marked and time-per-target score would be calculated. By subtracting part 2 from part 1 the attention score free from motor slowness could be calculated.

Map Mission is an accompaniment to the Sky Search. Children had to search a map to find as many target symbols as they could within one minute. The score was the number of targets correctly marked.

Sky Search DT was a combination of subtest Sky Search and another unused subtest. Children required completing the task in a similar fashion to Sky Search as well as keeping a count of “scoring” sounds. The score can be generated by subtracting the score in previous Sky Search by the weighted score in this task.

Walk, Don’t Walk requires children to move a pen on a paper path, following different instruction sounds. Score would be given by counting the number of correct steps.

4.2.5 Polosomnography (PSG)

All subjects with snoring who had undergone neurocognitive tests were invited to undergo a standard overnight polysomnography (PSG) using the Siesta ProFusion II PSG monitor (Compumedics Telemed PTY Ltd.; Abbotsford, Australia) in a dedicated pediatric sleep laboratory. In brief, the central and

occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram and electrocardiogram were recorded. The positions of the subject, respiratory airflow (oro-nasal thermal sensor and nasal air pressure transducer), work of breathing (chest and abdominal wall motion connected to piezoelectric transducers), arterial oxyhaemoglobin saturation with a signal averaging time of three seconds (SpO_2, by Ohmeda 3700 pulse oximeter, Boulder, CO, USA) and limb movements were measured. All data were scored by an experienced PSG technologist. Sleep stage, respiratory events and arousals were analyzed using standard criteria as recommended by the American Academy of Sleep Medicine.[222]

Obstructive apnea hypopnea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation >3% per hour of sleep. The oxygen saturation nadir (SpO2 nadir) was also noted. Arousal index (ArI) was defined as the total number of arousals per hour of sleep.

Subjects were classified into one of three SDB categories according to the PSG and questionnaire results.

- Group 1: healthy control group (with no history of snoring).
- Group 2: PS (OAHI<1 and history of snoring).
- Group 3: OSA group (OAHI≥1).

4.2.6 Statistical Analysis

Mean (standard deviation), median (interquartile range) and number (percentage) are presented for parametric, non-parametric and categorical data, respectively. Numerical and categorical variables between two independent groups were compared using Student t tests and chi square tests, respectively. Numerial data between three independent groups were compared using Kruskal–Wallis tests. Mann-Whitney tests with adjusted *p* values (significant at $p<.016$) were used for post hoc pairwise comparisons. The χ^2 test was used to assess the differences in proportion between three independent groups. Multiple χ^2 tests with adjusted *p* values (significant at $p<.016$) were used for multiple pairwise comparisons. Multiple linear regression analysis was used to assess the relationship between SDB category (control, PS and OSA) and neurocognitive variables, controlling for age, gender, and socioeconomic status. SDB category and gender were converted to dummy variables (0 for controls, 1 for PS, and 2 for OSA; 0 for female, 1 for male). Residual analysis was performed for each regression model to test the validity of model assumptions.

4.3 RESULTS

Of the 1,057 potential subjects who could be recruited, 54 children could not be contacted because of invalid contact information and 394 declined to take part. A total of 609 children aged 6 to 10 years were successfully recruited. One case was subsequently excluded as he was found to have Noonan syndrome with significant developmental delay. No significant differences were

found in demographic characteristics between children who took part in this study and those who did not, except for maternal age at pregnancy (Table 4.1).

Table 4.1 Comparison of characteristics between recruited (N=609) and non-recruited subjects (N= 448)

	Recruited	Not recruited	*p* value
Gestation week (weeks)	39±1	39±1	0.429
Birth Weight (kg)	3.2±0.4	3.2±0.4	0.800
Maternal age at pregnancy (year)	30±5	28±6	<0.001
Maternal Education level			0.142
Primary school or below	7.4	7.6	
F1 - F3	30.9	34.4	
High school	51.4	50.7	
University / College	10.3	7.4	
Paternal Education level			0.290
Primary school or below	9.5	6.0	
F1 - F3	36.7	33.3	
High school	40.3	52.5	
University / College	13.5	8.3	

4.3.1 Comparison between Snorers and Non-snorers

The demographic characteristics and neurocognitive tests results were compared between 204 snorers and 404 non-snorers. There were no significant differences between the two groups in all the neurocognitive functioning domains. We repeated the same analysis in boys and in girls separately. Boys with snoring had significantly lower total HK-WISC score and performance sub-

scale score than those without snoring. By contrast in girls no significant differences in neurocognitive measures were found between snorers and non-snorers (Table 4.2 and Table 4.3).

Table 4.2 Comparison of demographic characteristics and neurocognitive tests results between boys with and without snoring

	Snoring (n=126)	Non-snoring (n=202)	*p* value
Age (year)	8.1 (1.0)	8.0 (0.9)	.537
BMI (kg/m^2)	17.5 (3.1)	16.7 (2.7)	.013
BMI z-score	0.61 (0.98)	0.33 (0.98)	.012
Paternal education (%)			.540
Primary school and below	11.1	8.9	
F1-F3	32.5	39.1	
High school	43.7	37.6	
University/college	12.7	14.4	
Maternal education (%)			.834
Primary school and below	9.5	7.9	
F1-F3	34.1	30.7	
High school	47.6	51.5	
University/college	8.7	9.9	
Paternal NS-SEC class (%)			.306
Class 1	25.4	22.8	
Class 2	2.4	5.4	
Class 3	25.4	18.3	
Class 4	20.6	28.7	
Class 5	23.8	21.8	
Unemployed	2.4	3.0	
Maternal NS-SEC class (%)			.925
Class 1	19.0	16.3	
Class 2	14.3	13.9	
Class 3	3.2	3.0	
Class 4	1.6	3.5	
Class 5	15.1	14.9	
Unemployed	46.8	48.5	
Monthly family income (HK$) (%)			.195
<10,000	15.1	22.4	
10,000-40,000	73.8	64.7	
>40,000	11.1	12.9	

(Continued) Comparison of demographic characteristics and neurocognitive tests results between boys with and without snoring

	Snoring (n=126)	Non-snoring (n=202)	*p* value
HK-WISC			
Verbal scale score	111.8 (15.5)	116.0 (14.1)	.061
Performance scale score	108.9 (14.9)	114.0 (13.5)	.017
Total score	113.0 (12.2)	116.8 (12.2)	.007
HKLLT			
Learning	20.14 (6.09)	20.28 (6.05)	.840
Trial 3 intrusion errors	0.61 (0.88)	0.57 (0.81)	.660
Trial 3 perseveration errors	0.73 (0.99)	0.59 (0.83)	.180
Short delay recall difference	-1.67 (2.16)	-1.32 (2.10)	.144
Long delay recall difference	-1.73 (2.30)	-1.25 (2.19)	.060
TEA-Ch			
Sky search attention	10.38 (2.84)	10.20 (2.54)	.548
Sky search DT	8.43 (4.08)	8.64 (4.17)	.650
Map mission	9.35 (2.87)	9.88 (2.95)	.110
Walk, don't walk	9.78 (4.41)	9.88 (4.25)	.825

BMI, body mass index; NS-SEC, National Statistics Socio-Economic Classification; HK-WISC, Hong Kong-Wechsler Intelligence Scale for Children; HKLLT, Hong Kong List Learning Test; TEA-Ch, Test of Everyday Attention for Children.

Table 4.3 Comparison of demographic characteristics and neurocognitive tests results between girls with and without snoring

	Snoring (n=78)	Non-snoring (n=202)	*p* value
Age (year)	7.7 (0.9)	8.1 (0.9)	<.001
BMI (kg/m^2)	16.7 (2.4)	16.1 (2.5)	.072
BMI z-score	0.63 (0.92)	0.26 (1.03)	.005
Paternal education (%)			.150
Primary school and below	5.1	10.9	
F1-F3	41.0	35.3	
High school	35.9	42.8	
University/college	17.9	10.9	
Maternal education (%)			.158
Primary school and below	2.6	7.4	
F1-F3	35.9	27.2	
High school	47.4	55.4	
University/college	14.1	9.9	
Paternal NS-SEC class (%)			.132
Class 1	33.3	19.8	
Class 2	5.1	4.5	
Class 3	20.5	20.8	
Class 4	23.1	23.3	
Class 5	16.7	27.7	
Unemployed	1.3	4.0	
Maternal NS-SEC class (%)			.349
Class 1	23.1	15.8	
Class 2	15.4	16.8	
Class 3	2.6	6.4	
Class 4	2.6	1.0	
Class 5	9.0	14.4	
Unemployed	47.4	45.5	
Monthly family income (HK$) (%)			.726
<10,000	14.1	12.9	
10,000-40,000	73.1	77.2	
>40,000	12.8	9.9	

(Continued) Comparison of demographic characteristics and neurocognitive tests results between girls with and without snoring

	Snoring (n=78)	Non-snoring (n=202)	*p* value
HK-WISC			
Verbal scale score	117.6 (12.7)	114.5 (14.2)	.185
Performance scale score	112.5 (10.9)	110.8 (12.8)	.405
Total score	115.2 (11.5)	113.3 (12.5)	.232
HKLLT			
Learning	20.88 (6.68)	21.15 (6.01)	.745
Trial 3 intrusion errors	0.54 (0.98)	0.50 (0.84)	.742
Trial 3 perseveration errors	0.76 (1.18)	0.61 (0.97)	.301
Short delay recall difference	-0.79 (2.19)	-1.21 (2.24)	.165
Long delay recall difference	-0.90 (2.24)	-1.12 (2.36)	.467
TEA-Ch			
Sky search attention	9.82 (2.63)	9.47 (2.76)	.329
Sky search DT	8.38 (3.60)	7.56 (3.60)	.086
Map mission	9.67 (2.78)	9.50 (2.68)	.644
Walk, don't walk	9.38 (4.91)	9.87 (4.08)	.409

BMI, body mass index; NS-SEC, National Statistics Socio-Economic Classification; HK-WISC, Hong Kong-Wechsler Intelligence Scale for Children; HKLLT, Hong Kong List Learning Test; TEA-Ch, Test of Everyday Attention for Children.

4.3.2 Characteristics between non-snoring controls, PS and OSA groups

Among the 204 children with snoring, 121 cases refused to undergo sleep study, 34 cases lost contact, 3 cases had received an upper airway surgery, and one case was suspected to have autism. Therefore only 45 children underwent PSG in our study finally, of whom 27 were given a diagnosis of PS and 18 OSA. No one had PLMS. There were no significant differences in demographic and neurocognitive characteristics between the 45 participants and the 159 non-participants, except that the participants gained lower Sky search DT scores than the non-participants (Table 4.4). The comparisons of demographic and neurocognitive tests results are shown in Table 4.5. Children with OSA gained significantly lower scores in the Sky Search Attention test of TEA-Ch than non-snoring controls or children with PS. Nevertheless no significant worse performance in all the neurocognitive functioning tests was found in children with PS compared to non-snoring children.

Table 4.4 Characteristics of children with snoring who did and did not participate in the sleep study

	Participants (n=45)	Non-snoring (n=159)	*p* value
Age (year)	7.9 (1.1)	8.0 (0.9)	.528
Male gender (%)	51.1	64.8	.096
BMI z-score	0.58 (1.06)	0.63 (0.93)	.729
Paternal NS-SEC class (%)			.770
Class 1	31.1	27.7	
Class 2	4.4	3.1	
Class 3	22.2	23.9	
Class 4	20.0	22.0	
Class 5	17.8	22.0	
Unemployed	4.4	1.3	
Maternal NS-SEC class (%)			.639
Class 1	20.0	20.8	
Class 2	17.8	13.8	
Class 3	4.4	2.5	
Class 4	4.4	1.3	
Class 5	8.9	13.8	
Unemployed	44.4	47.8	
HK-WISC			
Verbal scale score	115.1 (14.5)	112.2 (14.7)	.356
Performance scale score	110.8 (13.9)	109.5 (11.6)	.644
Total score	112.8 (12.6)	114.2 (11.7)	.491
HKLLT			
Learning	19.4 (6.6)	20.7 (6.2)	.218
Trial 3 intrusion errors	0.7 (1.0)	0.6 (0.9)	.382
Trial 3 perseveration errors	0.6 (1.0)	0.8 (1.1)	.317
Short delay recall difference	-1.5 (2.4)	-1.3 (2.2)	.659
Long delay recall difference	-1.5 (2.3)	-1.4 (2.3)	.857
TEA-Ch			
Sky search attention	9.6 (2.8)	10.3 (2.8)	.136
Sky search DT	6.8 (3.9)	8.9 (3.8)	.002
Map mission	9.3 (3.0)	9.5 (2.8)	.586
Walk, don't walk	10.2 (4.5)	10.0 (4.6)	.811

Table 4.5 Comparisons between non-snoring controls, PS and OSA groups

	Non-snoring controls (N=404)	PS (N=27)	OSA (N=18)	*p* value
Age (year)	8.3 (7.4-8.8)	7.9 (7.1-8.9)	8.1 (6.6-8.9)	.403
Male gender (%)	50.0	48.1	55.6	.879
BMI (kg/m^2)	15.8 (14.6-17.5)	15.9 (15.1-17.4)	16.9 (14.6-20.4)	.255
BMI z-score	0.26 (-0.38-0.97)	0.49 (-0.16-1.08)	1.02 (-0.36-1.64)	.186
Paternal education				.361
Primary school and below	9.9	0	5.6	
F1-F3	37.2	33.3	38.9	
High school	40.2	40.7	44.4	
University/college	12.7	25.9	11.1	
Maternal education				.158
Primary school and below	7.7	3.7	5.6	
F1-F3	29.0	22.2	55.6	
High school	53.5	55.6	27.8	
University/college	9.9	18.5	11.1	
Paternal NS-SEC class				.847
Class 1	21.3	29.6	33.3	
Class 2	5.0	3.7	5.6	
Class 3	19.6	22.2	22.2	
Class 4	26.0	22.2	16.7	
Class 5	24.8	14.8	22.2	
Unemployed	3.5	7.4	0	
Maternal NS-SEC class				.807
Class 1	16.1	18.5	22.2	
Class 2	15.3	22.2	11.1	
Class 3	4.7	3.7	5.6	
Class 4	2.2	7.4	0	
Class 5	14.6	7.4	11.1	
Unemployed	47.0	40.7	50.0	

(Continued) Comparisons between non-snoring controls, PS and OSA groups

	Non-snoring controls (N=404)	PS (N=27)	OSA (N=18)	*p* value
HK-WISC				
Verbal scale score	116 (104-126)	108 (97-120)	121 (105-126)	.213
Performance scale score	112 (103-122)	112 (104-120)	105 (93-113)	.081
Total score	116 (107-124)	111 (102-121)	113 (101-121)	.495
HKLLT				
Learning	21 (16-25)	22 (16-26)	17 (14-25)	.390
Trial 3 intrusion errors	0 (0-1)	0 (0-1)	0 (0-1)	.661
Trial 3 perseveration errors	0 (0-1)	0 (0-1)	0 (0-1)	.790
Short delay recall difference	-1 (-3-0)	-2 (-4-0)	-1 (-2-0.5)	.419
Long delay recall difference	-1 (-3-8)	-2 (-3-0)	-1.5 (-2-0)	.377
TEA-Ch				
Sky search attention [b,c]	10 (8-12)	10 (8-13)	8 (6-10)	.012
Sky search DT	8 (6-11)	8 (3-10)	7.5 (4-9)	.203
Map mission	9 (8-12)	9 (7-12)	9 (7-10)	.476
Walk, don't walk	9 (6-12)	9 (6-12)	10 (7-16)	.475

[a] *p*<.016 controls vs PS;
[b] *p*<.016 controls vs OSA;
[c] *p*<.016 PS vs OSA

Multiple regression model showed that only TEA-Ch Sky Search DT score was negatively associated with SDB category (non-snoring control, PS and OSA) (β=-0.899, standard error=0.411, *p* value=.029), adjusted for age, gender and parental socio-economic status.

4.4 DISCUSSIONS

The current study failed to find significant differences in neurocognitive functioning between snoring and non-snoring children aged 6-9 years old recruited from the community. However in boys with snoring lower intelligence

scores compared to non-snorers was documented. By contrast girls with snoring had comparable neurocognitive performance as those without. Children with OSA had significant deficits in attention than controls and/or PS subjects. However neurocognitive function was not significantly impaired in primary snorers. There was a worsening trend in only one parameter measuring sustained attention with SDB severity increasing from control, PS, to OSA, independent of age, gender and parental socioeconomic status.

In contrary to our findings showing that snoring children did not have worse neurocognitive performance than non-snoring children, a few previous studies provided positive results in school-aged children. Several domains of neuropsychological function were reduced in the snoring group, including intelligence,[37, 135, 223] attention,[34, 37, 135, 223] memory,[135, 223] hyperactive behaviour,[28, 32, 34] and academic performance.[28, 30, 31] The discrepancy may be attributed to the following reasons. We only classified snoring frequency into two categories, i.e. “yes” or “no”, which is less accurate and the actual difference beween snoring and non-snoring is probably not very distinct for a community-based sample. By contrast, majority of the published studies analysed characteristics of habitual snorers as snored frequently or often, and recruited subjects from clinics so that their symptoms may be relatively more severe.

Interestingly boys were found to have reduced intelligence scores if he snored. It has been demonstrated that male gender is a significant risk factor for OSA in school-aged children.[94] Adult studies showed that oestrogen was

protective against upper airway collapse.[206] It is possible that our cohort of boys who snored were trending towards OSA, thus reduced intelligence scores compared to their female counterparts. Anyhow the average IQ scores in the snoring boys were still within the normal range and the difference was moderate, leaving the clinical significance of this difference in doubt.

PS was not shown to be associated with significant neurocognitive dysfunction in our study, which may be explained by its lack of intermittent hypoxia as seen in OSA. However a few research groups found that in school-aged children all severities of SDB even as mild as PS are at risk of developing impairment in neurobehavior (Table 4.6). This inconsistency may be attributed to reasons as follows. First, only a small number of snorers underwent PSG, and eventually we only had 27 PS cases. Thus there is inadequate statistical power to detect any subtle differences between groups. Second, we did not perform PSG in the non-snoring control group because of the restricted resources. Some of the parents did not share bedrooms with their children, we possibly misclassified some PS or OSA children as controls, causing the insignificant differences found between SDB and controls. Third, we utilized objective measurements to assess intellectual ability, attention, learning and memory, while it seemed to be more likely to detect significant neurocognitive deficits in children with SDB if using parent reported questionnaires.[97, 182, 186] It have been suggested that parents of children with less severe SDB who referred for a sleep clinic might have more psychological distress than parents

of children who presented with more severe SDB, which caused parents to describe their children's behaviours in a more negative way.[181, 182]

Although the neurocognitive function of children was not significantly affected by the presence of PS in our study, SDB was shown to have a dose-effect relationship with sustained attention. According to our subsequent chapter discussing about the natural history of PS, if a primary snorer remained obese/overweight, he/she would run higher risk of developing OSA with time. Thus preventing PS from worsening to OSA would also play an important role in preservation of normal neurocognitive function, and this obviously can only be clarified by longitudinal studies.

Table 4.6 Comparison to other studies conducted in school-aged children

First Author	Nation	Subjects	Recruitment	Measures	Results
Li	HK	27 PS; 18 OSA; 404 controls	From community	HK-WISC; HKLLT; TEA-Ch; Boston Naming Test; Grooved Pegboard Test	Children with OSA performed worse in some aspects of intelligence and attention tests. No significant deficits in PS children were found.
O'Brien[180]	USA	87 PS; 31 controls	Schools	Conners' Parent Rating Scale; CBCL; DAS; NEPSY	PS children performed worse on attention, social problems, anxious/depressive symptoms, cognitive abilities, certain language and visuospatial functions than the control subjects.
Miano[185]	Italy	13 PS; 31 OSA; 60 normal controls	PS/OSA from hospital; controls from schools	ADHD Rating Scale; WISC-III	The IQ estimates of PS and OSA were lower and the ADHD rating scale scores higher than those of controls.
Bourke[183]	Australia	59 PS; 24 mild OSA; 19 moderate to severe OSA; 35 controls	PS/OSA from hospital; controls from community	BRIEF; CBCL; WASI; WRAT-3; RCFT; COWAT	PS and OSA children had lower general intellectual ability and higher rates of impairment in executive and academic functioning.

(Continued) Comparison to other studies conducted in school-aged children

First Author	Nation	Subjects	Recruitment	Measures	Results
Hamasaki Uema[106]	Brasil	37 PS; 24 OSA; 20 controls	From hospital	RAVLT; WISC-III	PS and OSA children showed worse performance on learning and memory.
Beebe[97]	USA	17 PS; 9 mild OSA; 6 moderate to severe OSA; 17 controls	PS and OSA from hospital; controls from community	WISC–III; Stroop Test; GDS; NEPSY; WCST; BASC; BRIEF	Impairments was found on measures of behaviour regulation and some aspects of attention and executive functioning in PS and OSA subjects.
Brockmann[186]	Germany	69 PS, 23 UARS/OSA; 410 controls	From community	Hyperactivity–inattention score in a self-designed questionnaire; Academic performance report	Children with PS had more Hyperactive and inattentive behaviour, as well as poor school performance.
Biggs[182]	Australia	55 PS; 22 mild OSA; 16 moderate to severe OSA; 34 controls	From hospital	BRIEF; CogHealth	Results of the BRIEF revealed working memory deficits at all severities of SDB compared to controls. Results of CogHealth revealed no difference between SDB groups and controls.

HK-WISC, Hong Kong-Wechsler Intelligence Scale for Children; HKLLT, Hong Kong List Learning Test; TEA-Ch, Test of Everyday Attention for Children; CBCL, Child Behavior Checklist; DAS, Differential Ability Scales; NEPSY, Developmental Neuropsychological Assessment; ADHD, Attention-deficit hyperactivity disorder; WISC, Wechsler Intelligence Scale for Children; BRIEF, Behavior Rating Inventory of Executive Function; WASI, Wechsler Abbreviated Scale of Intelligence; WRAT-3, Wide Range Achievement Test-3; RCFT, Rey Complex Figure Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test; WISC-III - Wechsler intelligence scale for children; WRAML, Wide Range Assessment of Memory and Learning; GDS, Gordon Diagnostic System;WCST, Wisconsin Card Sorting Test; BASC, Behavioral Assessment Scale for Children.

In summary, adverse effects of snoring on neurocognitive functions could be demonstrated in boys only. Worsening sustained attention was found to associate with increasing severity of SDB. Well-designed prospective studies will be needed to examine the neurobehavioral consequences of PS in children.

CHAPTER 5

Sleep Architecture in School-aged Children with Primary Snoring

5.1 INTRODUCTION

Sleep architecture represents the cyclical pattern of sleep as it shifts between the different sleep stages, including non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Early in the night, one transitions from lighter sleep stages (stage 1) to deeper, slow-wave sleep (SWS), with REM sleep appearing during the latter part of the night.[222] Sleep architecture allows us to produce a picture of what an overnight sleep looks like, taking into account various depths of sleep as well as arousals to wakefulness. In paediatric population, it has been demonstrated that sleep efficiency, percentage of SWS and REM sleep decreases and percentage of lighter stage 2 sleep increases with age as well as Tanner stage.[224-226]

Sleep-disordered breathing (SDB) consists of a spectrum of diseases with severity ranging from primary snoring (PS) to obstructive sleep apnoea (OSA).[90, 91] OSA in school-aged children is associated with both neurocognitive dysfunction and behavioural problems.[213, 227] Apart from intermittent hypoxia, sleep fragmentation may account for the neurocognitive impairment demonstrated. Disturbance of normal sleep architecture is one form of sleep fragmentation. Unlike adults, overall sleep architecture is presumed preserved in children with OSA.[172, 228-234] However, more recent scientific research has provided contradicting evidence. Children with OSA were more likely to have

disturbed sleep architecture compared to children with PS or normal controls, including decreased percentage of SWS[185, 235, 236] and REM sleep[236-238] as well as increased percentage of stage 1/N1 sleep[184, 235, 237, 239] and REM latency.[185, 239] Furthermore these changes were reversible following treatment for OSA.[111, 240, 241]

PS defined as snoring in the absence of apnoea or hypopnoea during sleep is positioned at the milder end of the SDB spectrum, and several studies demonstrated that even PS might also exhibit neurobehavioral impairments as well as cardiovascular morbidities, while the mechanism is unclear.[106, 174, 175, 180, 183, 185, 186] Snoring is an upper airway breathing sound or noise resulted from partial or complete occlusion of the upper airway.[1] Little attention has been given on whether it will disturb normal sleep architecture. Majority of the few published studies have failed to reveal any significant differences in sleep architecture between primary snorers and normal controls.[97, 184, 185, 231] *Miano et al* found that primary snorers had a higher percentage of N1[235] and *Yang et al* demonstrated increased sleep latency in subjects with PS [239]. However these studies had small sample size and consisted of hospital-based subjects.

In this study, we aimed to investigate the sleep architecture of school-aged children with PS recruited randomly from the community. We hypothesized that the percentage of certain sleep stage and/or wakefulness after sleep onset in primary snorers would be different from that in non-snoring healthy controls.

5.2 METHODS

5.2.1 Subjects

Subjects aged between 6 and 13 years were recruited from 13 randomly selected schools.[94] In brief, parents were asked to complete a validated OSA screening questionnaire[242] (Appendix 7) that stratified children into high or low risk for OSA. All high risk and a randomly selected sample from the low risk group were invited to undergo overnight polysomnography (PSG) and clinical examination. Children were excluded if they had an intercurrent illness within 4 weeks of PSG, suffered from cardiac, renal or neuromuscular diseases, or if they had chromosomal abnormalities or had previously undergone upper airway surgery. Written informed consent and assent were obtained from the parents and subjects respectively. Approval by the ethics committee of the Chinese University of Hong Kong was obtained.

5.2.2 Polysomnography (PSG)

All recruited children underwent standard overnight PSG at a dedicated sleep laboratory with CNS 1000P polygraph (CNS Inc, Chanhassen, Minnesota, USA). In brief, the central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram and electrocardiogram were recorded. The positions of the subject, respiratory airflow (oro-nasal thermal sensor and nasal cannula connected to air pressure transducer), respiratory effortswork of breathing (chest and abdominal wall motion connected to piezoelectric transducers), arterial oxyhaemoglobin saturation with a signal averaging time of three seconds (SpO2, by Ohmeda

3700 pulse oximeter, Boulder, CO, USA) were measured. All data were scored by experienced PSG technologists. Sleep architecture was scored in 30s epochs according to the criteria outlined by Rechtschaffen and Kales.[243] The following parameters of sleep architecture were measured: total sleep time (TST), defined as time from sleep onset to the end of the final sleep minus wakefulness after sleep onset; sleep latency, defined as the time occurred from lights out to the first epoch of any sleep; the percentage of sleep period time in each sleep stage out of TST (Stage 1, 2, SWS = Stage 3 + Stage 4, and REM sleep); wakefulness after sleep onset (WASO), defined as the time spent awake during sleep period time (time from sleep onset to the end of final sleep).

Obstructive apnoea hypopnoea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation >3% per hour of sleep. The oxygen saturation nadir (SpO_2 nadir) was also noted. Arousal index (ArI) was defined as the total number of arousals per hour of sleep.

Subjects were classified into four groups according to the PSG and questionnaire results.

- Group 1: healthy control group (OAHI<1 and history of snoring<3 nights per week).
- Group 2: PS (OAHI<1 and history of snoring≥3 nights per week).
- Group 3: mild OSA group (OAHI 1–5).
- Group 4: moderate-to-severe OSA (OAHI≥5).

5.2.3 Anthropometry Assessment

The weight, height and Tanner stage of all subjects were assessed on the day of PSG. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Weight, height and BMI were converted to z-scores appropriate for age and gender, according to local reference.[193] Pubertal stage was evaluated using a self-assessment questionnaire to categorize Tanner stages.[202] Prepubertal was defined as Tanner stage 1, and pubertal defined as Tanner stage 2 or greater.

5.2.4 Statistical Analysis

All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois), and a *p* value <0.05 was considered statistically significant. The subjects were divided into four groups (healthy controls, PS, mild OSA and moderate-to-severe OSA) for comparison. The mean (SD), median (interquartile range [IQR]), and percentage were presented for parametric, nonparametric, and categorical data, respectively. Parametric with equal variances data were compared using one-way analysis of variance (ANOVA) and the Bonferroini's method was used for post hoc pairwise comparisons (*p*<0.05 statistically significant). Nonparametric and parametric without equal variances data were compared using the Kruskal-Wallis test and Mann-Whitney tests with adjusted *p* values (significant at *p*<.0083) were used for pairwise

comparisons. The chi square test was used to assess the differences in proportion between the four groups.

Multiple linear regression analysis was used to assess the relationship between SDB category (control, PS, mild OSA and moderate-to-severe OSA) and sleep architecture outcomes, controlling for age, gender, BMI z-score and puberty status. SDB category, gender and puberty status were converted to dummy variables (0 for controls, 1 for PS, 2 for mild OSA and 3 for moderate-to-severe OSA; 0 for female, 1 for male; 0 for prepubertal, 1 for pubertal). Residual analysis was performed for each regression model to test the validity of model assumptions.

Analysis of covariance (ANCOVA) models were used to further examine differences in sleep architecture variables among control, PS and OSA groups, after controlling for age, gender and BMI z-score, in prepubertal and pubertal children separately. Nonparametric variables were normalized via logarithmic transformation.

5.3 RESULTS

5.3.1 Comparison between controls, PS, mild OSA and moderate-to-severe OSA groups

A total of 619 children underwent overnight PSG (mean age 10.0±1.8 years; 396 (64.0%) boys; 524 (84.7%) prepubertal). The demographic and polysomnographic characteristics of the subjects with different SDB severities are compared in Table 5.1. The proportion of boys and BMI z-score increased

across the 4 groups. As expected, significant differences in OAHI, SpO_2 nadir, ODI and ArI were found across groups except between controls and subjects with PS. In terms of sleep architecture parameters, mild and moderate-to-severe OSA group had significantly higher percentage of stage 1 sleep compared to controls and PS group. However there were no significant differences in measures of sleep architecture between PS and control group.

Table 5.1 Demographic and polysomnographic data between SDB categories

	Controls (N=248)	PS (N=104)	Mild OSA (N=200)	Moderate-to-severe OSA (N=67)	*p* value
Age (year) [d]	10.0 (1.8)	9.5 (1.8)	10.2 (1.8)	9.8 (1.7)	.005
Male gender (%) [b,c]	54.4	64.4	71.0	77.6	<.001
BMI [b,c,d,e]	17.5 (3.1)	18.0 (3.3)	19.0 (3.9)	19.7 (3.6)	<.001*
BMI z-score [b,c]	0.29 (1.11)	0.59 (0.90)	0.68 (1.08)	0.99 (1.01)	<.001
Puberty (%)	17.7	9.6	17.5	9.0	.088
OAHI (/hr) [b,c,d,e,f]	0.12 (0-0.49)	0.16 (0-0.48)	1.3 (1.2-2.8)	8.2 (6.5-11.6)	<.001*
SpO_2 nadir (%) [b,c,d,e,f]	93 (92-94)	93 (92-95)	92 (90-93)	90 (88-92)	<.001*
ODI (/hr) [b,c,d,e,f]	0.12 (0-0.37)	0.22 (0-0.46)	0.53 (0.23-1.05)	3.04 (1.21-5.51)	<.001*
ArI (/hr) [b,c,d,e,f]	5.8 (4.4-7.5)	5.9 (4.4-8.0)	7.0 (5.4-8.4)	10.5 (8.2-14.9)	<.001*
TST (min)	470 (66)	474 (56)	467 (62)	465 (66)	.741
Sleep latency (min)	17.5 (10.5-29.5)	18.3 (10-27.5)	15.5 (9-33.4)	12.5 (6-27.5)	.271*
Stage 1 (%TST) [b,c,d,e]	6.0 (4.4-7.8)	6.0 (4.5-8.1)	7.5 (5.4-9.6)	8.4 (5.6-12.5)	<.001*
Stage 2 (%TST)	48.5 (5.8)	48.7 (5.6)	48.4 (5.2)	47.0 (5.9)	.205
SWS (%TST)	24.2 (6.3)	24.0 (5.5)	22.9 (5.6)	23.1 (4.9)	.108
REM sleep (%TST)	21.0 (4.5)	20.9 (3.7)	20.8 (4.3)	20.2 (4.9)	.579
WASO (%SPT)	8.9 (5.1-13.5)	8.7 (6.3-12.0)	9.0 (5.6-14.8)	9.6 (6.2-13.3)	.451*

Mean (SD), median (IQR) and percentage (%) are presented for parametric, non-parametric and categorical data, respectively.
PS: primary snoring; OSA: obstructive sleep apnoea; BMI: body mass index; OAHI: obstructive apnoea hypopnoea index; SpO_2 nadir: oxygen saturation nadir; ODI: oxygen desaturation index; ArI: arousal index; TST: total sleep time; REM: rapid eye movement; SWS: slow wave sleep; WASO: wakefulness after sleep onset; SPT: sleep period time
* Kruskal-Wallis test was used.
[a] significant difference between controls and PS
[b] significant difference between controls and mild OSA
[c] significant difference between controls and moderate-to-severe OSA
[d] significant difference between PS and mild OSA
[e] significant difference between PS and moderate-to-severe OSA
[f] significant difference between mild OSA and moderate-to-severe OSA

In all of the measures of sleep architecture, after controlling for age, gender, BMI z-score and puberty status, stage 1 sleep (%TST) had significantly positive association while SWS (%TST) had significantly negative association with SDB categories ranging from normal control, PS, mild to moderate-to-severe OSA,. As expected, age and puberty status exerted an effect on sleep architecture (Table 5.2).

Table 5.2 Multiple regression model for the association between sleep architecture and SDB category (controls, PS, mild OSA and moderate-to-severe OSA) adjusted for age, gender, BMI z-score and puberty (N=619)

Outcome variable	Predictor variable	β	Standard error	*p* value
Stage 1 %TST	SDB category	0.91	0.13	<.001
	Age	0.39	0.09	<.001
	BMI z-score	0.33	0.13	.012
SWS %TST	SDB category	-0.62	0.22	.004
	Age	-0.81	0.15	<.001
	Puberty	-1.79	0.74	.016

5.3.2 Sleep architecture in prepubertal and pubertal subjects

We further divided the whole cohort into prepubertal and pubertal subjects and compared the sleep architecture measures between controls, PS and OSA groups respectively, after adjusting for age, gender and BMI z-score. The sample size was as follows: 204 controls, 94 PS and 226 OSA in prepubertal children; 43 controls, 11 PS and 41 OSA in pubertal children.

We found that in prepubertal subgroup, stage 1 sleep (%TST) and SWS (%TST) were significantly different between healthy normal controls, children with PS and OSA. And in pubertal subgroup, stage 1 sleep (%TST) and ln WASO (%SPT) were significantly different between SDB severity categories. Nevertheless in prepubertal children, the significantly higher percentage of stage 1 sleep and lower percentage of SWS were only present between OSA and non-OSA group (control or PS). The differences between controls and PS did not reach statistical significance. However in pubertal children, significantly increased stage 1 sleep (%TST) and ln WASO (%SPT) existed not only between OSA and non-OSA group but also between PS and control group (Figure 5.1A-D).

Figure 5.1A Mean with 95% CI (confidence interval) of stage 1 sleep in prepubertal subjects adjusted for age, gender and BMI z-score

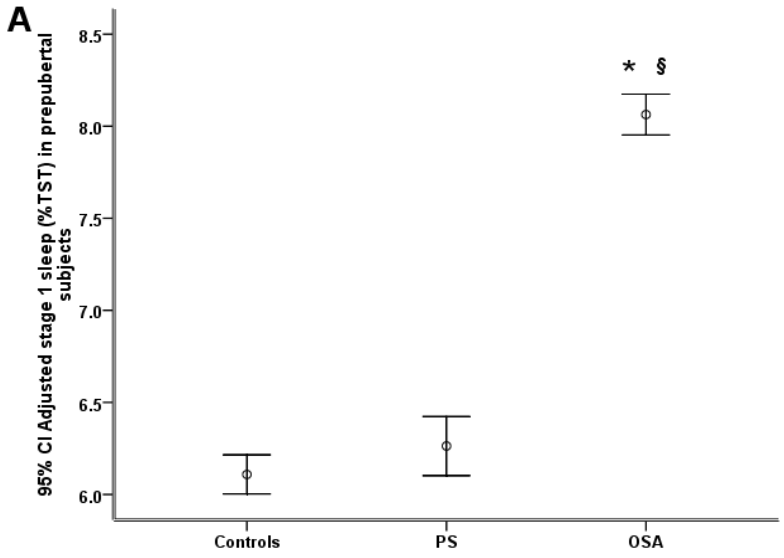


Figure 5.1B Mean with 95% CI (confidence interval) of SWS in prepubertal subjects adjusted for age, gender and BMI z-score

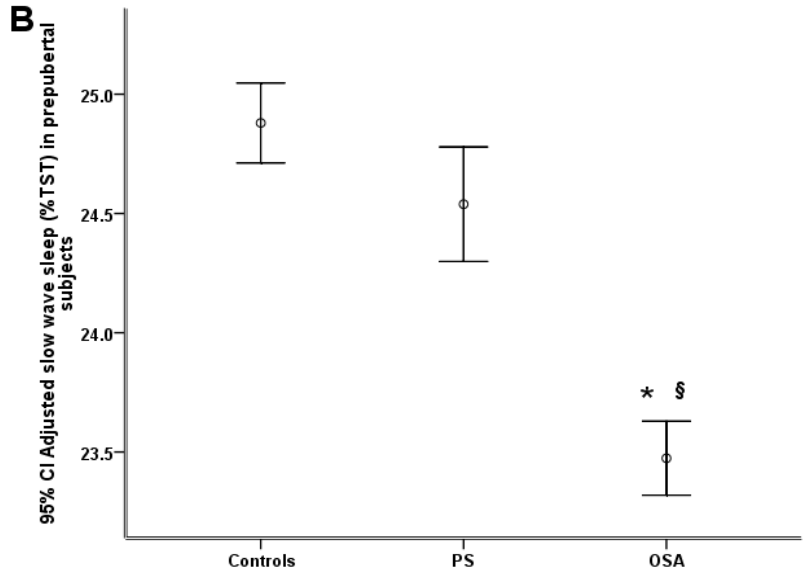


Figure 5.1C Mean with 95% CI (confidence interval) of stage 1 sleep in pubertal subjects adjusted for age, gender and BMI z-score

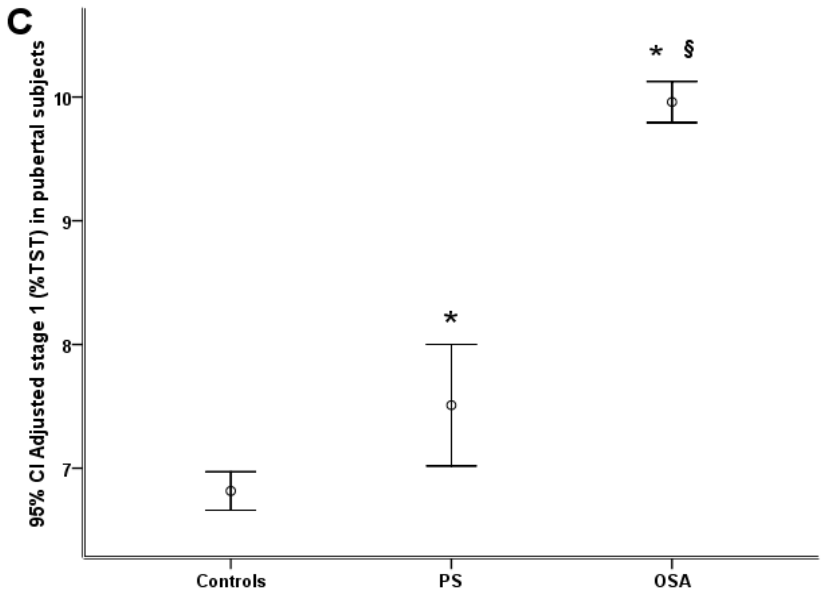
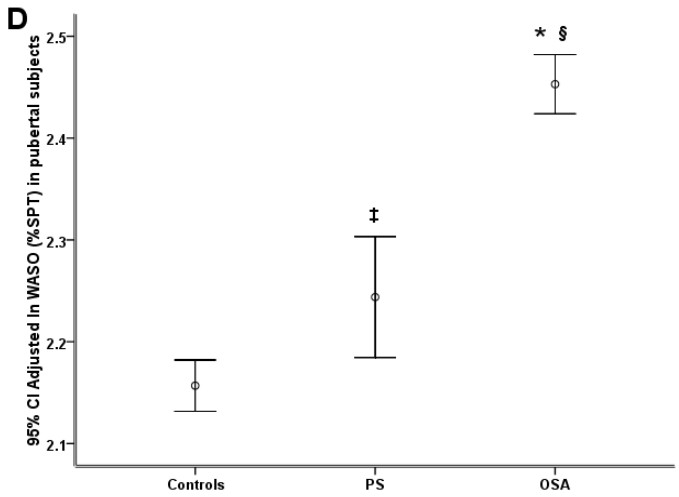


Figure 5.1D Mean with 95% CI (confidence interval) of ln WASO in pubertal subjects adjusted for age, gender and BMI z-score



* p<.01 compared with controls； ‡ p<.05 compared with controls；§ p<.01 compared with PS

5.4 DISCUSSIONS

In this large community-based study, no significant disruption of sleep architecture in children aged 6-13 years with primary snoring was found when compared to nonsnoring healthy children. After controlling for age, gender, BMI z-score and puberty status, increased percentage of stage 1 sleep and decreased percentage of SWS were independently associated with SDB severity from normal control, PS, mild to moderate-to-severe OSA. In prepubertal children, there were no significant differences in adjusted sleep architecture between PS and normal subjects. However in pubertal children, adjusted percentage of stage 1 sleep and WASO were both significantly elevated in primary snorers compared to non-snoring children.

In general, our findings were consistent with published literature comparing PS with non-snoring healthy controls (Table 5.3), i.e. sleep architecture was not impaired in school-aged children with PS until the condition progressed to the development of OSA, especially in prepubertal children. Based on research studies investigating the effects of OSA on sleep architecture in children, it was proposed that arousals secondary to intermittent apnoea and/or hypopnoea during sleep led to sleep fragmentation.[111, 235-238] Sleep architecture is therefore conserved in subjects with PS which does not cause much arousals in the absence of apnoeas or hypopnoeas.

The severity of SDB (controls, PS, mild OSA and moderate-to-severe OSA) was demonstrated to have a dose-response relationship with stage 1 sleep

(%TST) and SWS (%TST). Similar results were also found by other research groups.[97, 184, 239, 244]

The findings of our study suggested that in pubertal teenagers, PS, even without apparent apnoeas or hypopnoeas, had significantly impaired sleep architecture including increased percentage of stage 1 sleep and WASO. Studies examining whether pubertal adolescents were more prone to have disruption of sleep architecture than prepubertal children were lacking. It is known that adults have more arousals or wakefulness than children,[245] suggesting that the threshold of arousals triggered by hypoxia or hypercapnia might decrease with age. We also found that WASO (%SPT) was significantly higher in pubertal adolescents compared to prepubertal children (11.2 (6.6-16.7) vs. 8.6 (5.4-12.9), p=.002). It remains unclear whether hormone changes occurring in puberty might have an impact on arousal or awakening during sleep. Small sample size of pubertal subjects in our study could have led to selection bias, thus future studies exploring the effect of puberty on sleep architecture in SDB are still needed.

Stage 1 is light sleep which occurs most often in the transition from wakefulness to the other sleep stages or following body movements during sleep. If movement arousals occur, stage 2 or stage REM is very likely to change to stage 1 according to R&K scoring rules.[243] Therefore the elevation of stage 1 was possibly due to cortical or movement arousals and awakenings secondary to intermittent complete or partial hypoxia during sleep. Evidence showed that higher percentage of Stage 1 sleep adversely impacted learning

and memory in children.[101] Increased WASO represents reduced sleep efficiency. A study conducted in healthy adults by our research group showed that lower sleep efficiency was correlated with higher 24-h urinary catecholamines suggesting increased sympathetic activity, which plays a critical role in the pathogenesis mediating cardiovascular complications.[246] SWS facilitated the assimilation of new knowledge[247] and higher percentages of SWS were associated with better neurocognitive functioning.[97] Thus the significantly increased percentage of stage N1 and WASO as well as the trend in reduction in percentage of SWS found in this study may explain some of the neurocognitive deficits and cardiovascular morbidities seen in children with PS.

One limitation of this study is that subtle EEG changes might not have been detected with our conventional monitoring, more sophisticated techniques such as spectral analysis of EEG frequency,[228] cyclic alternating pattern (CAP) of NREM[244] or REM density[248] are needed.

In conclusion, PS did not exert significant adverse influences on normal sleep architecture in prepubertal school-aged children. Nevertheless pubertal adolescents with PS had higher stage 1 sleep and WASO than non-snoring healthy controls.

Table 5.3 Comparison of our findings and previous studies on sleep architecture of PS in children

Author	*Nation*	*Age*	*Sample size of primary snorers*	*Sample size of normal controls*	*Scoring rule*	*Difference in sleep architecture between PS and controls*
Bourke et al[184]	Australia	7-12 yr	59	35	R&K[243]	Not significant
Beebe et al[97]	US	6-12 yr	17	17	R&K	Not significant
Khadra et al[231]	US	7-13 yr	32	14	R&K	Not significant
Miano et al[185]	Italy	8.6±1.9 yr	13	60	AASM[222]	Not significant
Yang et al[239]	Australia	7-12 yr	50	30	R&K	PS had longer sleep latency
Miano et al[235]	Italy	6.2±3.2 yr	26	10	R&K AASM	R&K: Not significant; AASM: PS had higher N1%

CHAPTER 6

Association between Habitual Snoring and Ambulatory Blood Pressure in Children

6.1 INTRODUCTION

Snoring is the most important symptom of paediatric sleep-disordered breathing (SDB). SDB includes a spectrum of diseases, from primary snoring (PS) to obstructive sleep apnoea (OSA) positioned at its mild and severe end respectively.[90, 91]

OSA is characterized by recurrent hypoxia and repetitive arousals resulting from intermittent airway occlusion. Both events are proposed to mediate sympathetic activation that may overspill into daytime leading to hypertension.[249, 250] *Marcus et al* was the first to report that children with OSA had significantly higher diastolic blood pressure (BP) than children with PS.[251] *Bixler et al* demonstrated that nighttime on-the-spot systolic BP was significantly elevated in OSA children compared to normal controls and was positively correlated with apnoea hypopnea index (AHI).[252] Similarly *Enright et al* and *Kohyama J et al* both found a positive association between OSA severity and systolic as well as diastolic BP.[149, 150] Two intervention studies showed that the reduction or increase in daytime casual BP after adenotonsillectomy occurred in parallel with the resolution or recurrence of OSA disease.[167, 253] Later on *Amin et al* utilized 24-hour ambulatory BP (ABP) monitoring and revealed that children with OSA had significantly greater BP variability during wakefulness

and sleep and a smaller nocturnal dipping of mean BP than children with PS.[148] Subsequently *Amin et al* and *Leung et al* both found significant increases in wake and sleep BP levels in those whose AHI >5/hr.[147, 151] Our research group carried out a study involving a large community-based sample and found that children with either mild or moderate-to-severe OSA had significantly higher BP than normal healthy children during both sleep and wakefulness. Multiple linear regression revealed a significant association between oxygen desaturation index (ODI) and AHI with daytime and nocturnal BP, respectively, independent of obesity.[152] *Ng et al* demonstrated that significant decrease in overall 24h DBP load was achieved after AT in children who were cured of OSA.[254]

On the other hand, dysregulation of BP has also been increasingly noted in children with PS which is defined as snoring without apnoea, frequent arousals or gas exchange abnormalities.[170] *Kwok et al* found that children with PS had increased casual daytime diastolic BP and reduced arterial distensibility.[173] Our research group further demonstrated that nighttime diastolic BP was elevated in normal weight children with PS compared to healthy controls.[175] A recent study using continuous BP recordings made by finger photoplethysmography reported that PS group had higher waketime systolic and diastolic BP than controls.[255]

Therefore the whole SDB continuum with severity ranging from PS to OSA can exert adverse effects on BP regulation. Since snoring is the most common symptom of SDB and habitual snoring is one of the criteria in defining PS and OSA,[2, 256] we hypothesized that the presence of habitual snoring on its own

would be an independent risk factor for BP dysregulation. One previous study has failed to demonstrate significant difference in BP between habitual snorers and non-habitual snorers, however only daytime casual BP was measured in the study.[257] Hence we aimed to re-examine the association between habitual snoring and BP assessed by 24h ABP in children recruited from the community.

6.2 METHODS

6.2.1 Subjects and Study Design

This study was carried out concurrently with a community-based study aiming to develop 24-hour ambulatory BP reference values for Hong Kong Chinese children aged 8-18 years. Healthy Chinese primary and secondary school children who are Hong Kong permanent residents were eligible for inclusion. Children were excluded from the study if they were reported by their parents to have cardiovascular, renal or endocrine diseases, chromosomal abnormalities, or if they were taking any medication that can affect BP.

A two-stage cluster sampling method was used. With the assistance of the Education Bureau, a sampling frame of all primary and secondary schools in Hong Kong was complied. The first stage involved selection of schools and the second stage the students. All students who joined the study were randomly selected by computer generated numbers. Consequently a total of 14 primary and 18 secondary schools participated. Informed assent and consent were obtained from the subjects and their parents respectively before ABP monitoring. The study was approved by the Joint Clinical Research Ethics

Committee of the Chinese University of Hong Kong and New Territories East Cluster.

6.2.2 Questionnaire

The parents of all participants were invited to complete a self-designed sleep symptom questionnaire (Appendix 3). Snoring frequency was assessed by a single question, namely “How often did he/she snore during sleep?” and was rated on a 4-point scale: 0=never; 1=less than one night per month; 2=one to two nights per week; 3=three nights or more per week. The subjects were divided into three groups according to snoring frequency for comparisons: (1) non-snorers, those reporting “never”; (2) occasional snorers, those reporting “< 1 night per month” or “1-2 times per week”; and (3) habitual snorer, those reporting “≥ 3 nights per week”. Parents were asked whether they had history of hypertension. We defined parental hypertension as father and/or mother with positive history of hypertension.

6.2.3 Anthropometric Measurements

A team of three trained research staff visited each selected school on a pre-arranged date to collect the anthropometric data. All instruments were validated following the standard methods recommended by the manufacturers, and the balances were zero calibrated. Standing height without shoes was measured using a height measuring instrument (seca 217, UK) to the nearest 0.1 cm. Body weight was measured with the lightest clothing to the nearest 0.1

kg by an electronic weighing scale (Tanita BF-522, Japan). BMI was calculated as weight/height^2 (kg/m^2) and was translated to BMI z-score according to local reference data.[193] Children were defined as overweight if their BMI z-score was ≥ 1.036, corresponding to the 85th percentile (relative to age and gender). All participants completed a validated self-reported Pubertal Development Scale for pubertal staging.[202] Subjects were categorized as prepubertal, defined as Tanner stage 1, or pubertal, defined as Tanner stage 2 or greater.

6.2.4 ABP Measurements

Typically, school morning session began at about 8 AM and ended at about 1 PM. The ABP monitoring was setup during break-time at around 10:00-10:30 AM and removed from the students after 24 hours. ABPM readings were obtained using the nondominant arm with TM2430 (A&D, Inc., Tokyo, Japan) and the appropriate cuff size was determined by the mid-arm circumference based on standard techniques.[258] This device employs the oscillometric method to measure systolic and diastolic pressures as well as heart rate, and has been validated for use in children.[259] The ABP monitoring readings were obtained every 30 min during the 24-hr recording period. All subjects were asked to maintain their usual activity but to remain still during daytime measurements. Furthermore, subjects and parents were asked to record the time the subjects went to bed, their wake time, as well as exercise periods and their sleep quality in a diary. The duration of day and night periods was established individually for each child based on their completed diary. At the

end of the recording, the measurements were downloaded onto a laptop computer for analysis. The first reading at the beginning of sleep was not included in the analysis for improving the accuracy of true sleep time. Only ABP profiles with at least 40 recordings, including at least 8 readings during sleep, was accepted. Recordings were automatically rejected if systolic blood pressure (SBP) is >220 or <60mmHg or if diastolic blood pressure (DBP) >120 or <35mmHg or if heart rate (HR) >180 or <40 beats/min. [258]

All mean BP variables were converted into BP z-scores using the ‘‘LMS’’ reference values (relative to gender and height) using our own data in this study. In brief, we had derived height and gender specific estimates of the distribution median (M), coefficient of variation (S) and degree of skewness (L), which were estimated by a maximum likelihood of curve fitness technique.[260] These estimated parameters were used to transform the skewed data to normality, giving a more accurate ABP z-score. Hypertension were defined as mean BP values > 95th percentiles of our own ABP data. Nocturnal dipping of systolic and diastolic BP were derived by calculating the difference between mean wake time and mean sleep time BP and expressed as a percentage of mean wake time BP. Subjects with nocturnal BP dipping less than 10% were defined as non-dippers.[261]

6.2.5 Statistical Analysis

Data were presented as mean (standard deviation) and number (percentage) for continuous and categorical data, respectively. The trends of

characteristics across snoring frequency groups were analysed using Analysis of variance (ANOVA) tests for continuous variables and linear-by-linear association χ^2 tests for categorical variables, respectively. Multiple linear and logistic regression analyses was subsequently performed to further confirm the association between presence of habitual snoring and continuous and categorical ABP measures respectively, after controlling for age, gender and BMI z-score. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois), and a *p* value <0.05 was considered statistically significant.

6.3 RESULTS

A total of 1,447 subjects were included in this study. The demographic characteristics and ABP measures across the non-snorers, occasional snorers and habitual snorers are shown in Table 1 and Table 2, respectively. The proportion of boys and parental history of hypertension, BMI z-score, wake time SBP, wake time SBP z-score and sleep time SBP z-score increased and age decreased across the three groups.

However after adjustment for age, gender, BMI z-score and parental hypertension, the presence of habitual snoring was not associated with any ABP values and nocturnal BP dipping. Neither could it predict the presence of hypertension during wakefulness or sleep and BP non-dipper.

Similar statistical analysis was repeated for normal weight and overweight subjects respectively. There were no significant independent associations between presence of habitual snoring and ABP variables, either.

Table 6.1 Demographic characteristics of different snoring frequency groups

	Non-snorers (n=837)	Occasional snorers (n=479)	Habitual snorers (n=131)	*p* value for trend
Age (year)	13.2 (2.8)	12.5 (2.8)	12.4 (2.7)	<.001
Male gender (n(%))	365 (43.6)	260 (54.3)	86 (65.6)	<.001
Weight (kg)	45.5 (12.9)	44.9 (15.1)	50.2 (17.5)	.033
Height (cm)	153.5 (13.6)	150.7 (14.1)	152.3 (13.4)	.011
Waist circumference (cm)	65.5 (33.4)	65.1 (12.1)	69.9 (12.4)	.235
BMI (kg/m^2)	19.0 (3.3)	19.2 (4.0)	21.1 (4.8)	<.001
BMI z-score	0.20 (1.00)	0.37 (1.04)	0.82 (1.12)	<.001
Puberty (%)	733 (87.6)	408 (85.2)	115 (87.8)	.539
Parental hypertension (n(%))	107 (12.8)	80 (16.7)	28 (21.4)	.004

Table 6.2 ABP values of different snoring frequency groups

	Non-snorers (n=837)	Occasional snorers (n=479)	Habitual snorers (n=131)	*p* value for trend
During wakefulness				
SBP (mmHg)	120.1 (10.1)	121.3 (9.8)	122.9 (9.8)	.001
SBP z-score	-0.04 (1.02)	0.06 (1.03)	0.12 (0.97)	.036
DBP (mmHg)	73.0 (7.0)	72.8 (6.7)	73.5 (7.2)	.746
DBP z-score	0.00 (1.02)	-0.02 (1.00)	0.05 (1.10)	.844
SHT (n(%))	45 (5.4)	36 (7.5)	9 (6.9)	.190
DHT (n(%))	53 (6.3)	25 (5.2)	7 (5.3)	.441
During sleep				
SBP (mmHg)	101.2 (8.2)	101.7 (8.4)	102.0 (8.9)	.193
SBP z-score	-0.08 (1.01)	0.07 (1.02)	0.05 (1.00)	.015
DBP (mmHg)	57.1 (5.6)	56.8 (5.8)	57.1 (5.8)	.560
DBP z-score	0.01 (1.01)	0.00 (1.05)	0.02 (1.05)	.996
SHT (n(%))	31 (3.7)	22 (4.6)	6 (4.6)	.443
DHT (n(%))	48 (5.7)	36 (7.5)	5 (3.8)	.944
Nocturnal dipping				
SBP dipping (%)	19.3 (11.8)	19.8 (11.2)	21.2 (11.4)	.093
DBP dipping (%)	21.2 (9.4)	21.5 (8.7)	21.9 (9.3)	.382
SBP non-dipper (n(%))	198 (23.7)	101 (21.1)	22 (16.8)	.062
DBP non-dipper (n(%))	99 (11.8)	46 (9.6)	15 (11.5)	.449

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SHT, systolic hypertension; DHT, diastolic hypertension.

6.4 DISCUSSIONS

In the present study, we reported the absence of independent correlation between ABP measurements and habitual snoring in a community-based sample of children. After adjustment for age, gender, BMI z-score and parental hypertension, the presence of habitual snoring could not predict dysregulation of ABP values.

Children with habitual snoring could usually be classified as one of two entities across the SDB spectrum, namely either PS or OSA, according to their overnight sleep study result. OSA is present if one's obstructive apnoea hypopnoea index (OAHI) exceeds 1/hr, which is currently the most commonly used diagnostic criteria although unstandardized.[142, 173, 174, 251, 255, 262] For habitual snorers who were diagnosed as PS, only three studies conducted in the paediatric population reported its correlation with elevated BP. *Kwok et al* demonstrated that children with PS had increased daytime systemic BP and reduced arterial distensibility which may jeopardize long-term cardiovascular health, regardless of BMI.[173] This study, however, utilized on-the-spot BP measurement which could not reflect the whole picture of BP fluctuation and increased the possibility of random effects. Our research group investigated 24-h ABP in normal weight children with PS recruited from the community. Nevertheless only nighttime DBP was significantly higher in children with PS compared with non-snoring controls after adjusting for age, sex, and BMI, with a mean difference of only 3.2 mmHg.[175] A more recent study recorded BP continuously overnight using finger photoplethysmography and revealed that

BP during awake before sleep onset and during overnight sleep was elevated by around 10 mmHg in the PS group compared with the control group.[255] Photoplethysmographic approach for continuous estimation of BP maybe a more sensitive way to pick up subtle BP differences.[263]

As far as BP in OSA is concerned, OSA children have been demonstrated to have higher BP value than normal controls or PS subjects, but this is not the case across the OSA severity spectrum. A number of studies verified that BP levels had a positive correlation with AHI or respiratory disturbance index (RDI).[149, 150, 152, 252] Other studies however, only found significantly increased BP in moderate or severe OSA cases.[147, 150, 151]

Overall, there is insufficient data exploring BP abnormalities in PS subjects and cohort or intervention studies which can show causal relationships are lacking. Considering the weak or modest effect size of presence of PS on BP generated from existing cross-sectional studies, therefore the adverse impact of PS on BP is still inconclusive at present. Moreover even if an individual had OSA, he/she might not have evident elevated BP if the disease was mild. Therefore it is possible that simple snoring on its own does not lead to BP dysfunction.

Our finding is similar to another study showing that habitual snorers did not have higher morning systolic or diastolic BP than non-habitual snorers in a community sample of children.[257] The authors attributed this negative finding to not performing PSG. Many of the habitual snorers were likely to only have primary snoring, or some habitual snorers with SDB might have been

misclassified as non-snorers, which would have attenuated possible BP differences between the two study groups. Therefore PSG will still be necessary to identify genuine cases with OSA (especially moderate-to-severe cases) who are at higher risk for developing hypertension. Additionally, primary snoring possibly can be further divided into various severities, using advanced technologies such as EEG spectral analysis, peripheral arterial tonometry and pulse transit time which may help to identify subtle abnormalities in respiratory parameters and/or arousals.[264, 265] Therefore lumping all habitual snorers under one umbrella term may not be correct. Nevertheless this assumption requires corresponding studies to verify it in the future.

One limitation of this study was that snoring was not quantified by objective assessment tool which is a limitation shared with other community-based survey studies. Snoring group allocation was based on information provided by the parent-complete questionnaire alone. Parents might underestimate the frequency of snoring of their children if they did not sleep in the same bedroom. Such misclassification might have attenuated possible BP differences between the study groups. However as a result of restricted resources, applying overnight monitor to record snoring was less practical for a large population survey.

In conclusion, ABP was not significantly different between children with and without habitual snoring, after controlling for age, gender and BMI z-score. Screening of habitual snoring purely by questionnaire was unable to predict children at risk of having ABP abnormalities.

CHAPTER 7

Endothelial Function in Children with Primary Snoring

7.1 INTRODUCTION

Childhood obstructive sleep apnoea (OSA) has been found to associate with cardiovascular abnormalities in children,[96] including left and right ventricular hypertrophy and dysfunction,[142-146] elevation of blood pressure (BP),[151, 152, 251, 252] altered BP rhythm,[148] and impairment of autonomic cardiac modulation.[266-268] In contrast to OSA, primary snoring (PS) which is defined as snoring without apnoea, frequent arousals or gas exchange abnormalities[170] is positioned at the milder end of the sleep disordered breathing (SDB) severity continuum,[177] and treatment is usually not prescribed.[178] However recent evidence suggest that childhood PS is also related to cardiovascular consequences and should not be considered as completely benign.[179] *Kwok et al* found that children with PS had increased casual daytime BP and reduced arterial distensibility.[173] Our research group further demonstrated that nighttime BP was elevated in normal weight children with PS.[175]

Endothelial dysfunction is an early indicator of cardiovascular morbidities.[269, 270] Functional and structural disruption of the endothelium could be induced by intermittent hypoxia in the presence of OSA.[271, 272] Ultrasonographic assessment of endothelial-dependent flow mediated vasodilation (FMD) of the brachial artery is the gold standard in assessing endothelial function. It is safe and well-tolerated in both adults and children.[273,

[274] Indeed, abnormal FMD has been reported in adults with OSA and improvement documented after treatment with continuous positive airway pressure (CPAP).[275-277] Only a paucity of studies have explored whether OSA adversely impacts endothelial function in children. *Gozal et al* first reported that postocclusive hyperemia was blunted in children with OSA, and such altered endothelial function was reversible after adenotonsillectomy.[278] A few studies further confirmed that there was a dose-dependent increase in time to peak regional blood-flow response post-occlusion release (Tmax) with increasing severity of OSA,[279-282] and several circulating inflammatory microparticles levels were associated with the changes in endothelial function.[278, 279, 281]

On the other hand, we are aware of only one study that investigated endothelial function in children with PS. Children aged 6-18 years with PS were found to have reduced FMD compared to non-snoring controls, independent of obesity.[174] Whether a dose-dependent relationship exists between FMD abnormality across the SDB severity spectrum is unknown.

We therefore carried out this study to examine this important yet poorly defined issue of endothelial function in children with SDB. To remove the effect of obesity which is a well-known risk factor for cardiovascular diseases, we recruited only non-obese subjects. We hypothesized that the severity of SDB ranging from non-snoring controls, PS, to OSA would have a dose-effect relationship with increasing endothelial dysfunction.

7.2 METHODS

7.2.1 Subjects and Study Design

Chinese children with habitual snoring (snoring frequency≥3 nights/week) aged 6-18 years who attended our paediatric chest and sleep disorder clinic were consecutively recruited for this study. Non-snoring controls (never snoring or snoring frequency<1 nights/month) were recruited from siblings of patients attending our clinic or participants of our growth survey. Written informed consent and assent were obtained from parents and subjects respectively. The exclusion criteria included obesity (see definition in the section of anthropometry assessment), previous treatment for OSA, presence of structural heart disease, medical history of hypertension, dyslipidemia, diabetes mellitus, genetic syndrome, congenital or acquired neuromuscular disease, premature birth, intrauterine growth retardation, active smoking and acute illness within 4 weeks of recruitment. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

All participants underwent nocturnal polysomnography (PSG) and endothelial function evaluation on the same day.

7.2.2 Anthropometry Assessment

Their weight and standing height were measured with a calibrated weighing scale and stadiometer, respectively. Body mass index (BMI) was calculated as weight/ height^2 (kg/m^2). BMI were converted to z-scores appropriate for age and gender, according to local reference.[193] Obese children were defined as a BMI z-score ≥1.645, corresponding to the 95th percentile.

7.2.3 Polysomnography (PSG)

All recruited children underwent a standard overnight PSG at a dedicated sleep laboratory with CNS 1000P polygraph (CNS Inc, Chanhassen, Minnesota, USA). In brief, the central and occipital electroencephalogram (EEG), bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram and electrocardiogram were recorded. The positions of the subject, respiratory airflow (oro-nasal thermal sensor and nasal cannula connected to air pressure transducer), respiratory effortswork of breathing (chest and abdominal wall motion connected to piezoelectric transducers), arterial oxyhaemoglobin saturation with a signal averaging time of three seconds (SpO2, by Ohmeda 3700 pulse oximeter, Boulder, CO, USA) were measured. All data were scored by experienced PSG technologists according to the American Academy of Sleep Medicine (AASM) 2007 pediatric polysomnography scoring criteria.[222]

Obstructive apnea hypopnea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation >3% per hour of sleep. Arousal index (ArI) was defined as the total number of arousals per hour of sleep. The oxygen saturation nadir (SpO_2 nadir) was also noted.

Subjects were classified into three SDB severity groups for comparisons:

- Group 1: OSA group (habitual snoring and OAHI≥1).
- Group 2: PS group (habitual snoring and OAHI<1).

- Group 3: control group (non-snoring and OAHI<1).

7.2.4 Endothelial Function

The assessment was carried out in a quiet, temperature-controlled room. All subjects abstained from food, including caffeine for at least 6 hours before the study. The diameter of the brachial artery was measured on B-mode ultrasound images (i) at rest, (ii) in response to reactive hyperemia, which was induced by inflation of a BP cuff placed around the lower-arm to a pressure of 220 mmHg for 4–5 min, followed by rapid deflation, and (iii) after sublingual nitroglycerin (400 micrograms spray), using a linear array transducer (L10-5 median frequency, 7.5 MHz) and Advanced Technology Laboratories 3000 ultrasound system. To minimize variability, all measurements were taken at end diastole identified by the R wave on ECG, and the average of three measurements along the vessel was taken. The full procedure was described in details previously.[269] All ultrasonographic scans were performed by the same investigator who was blinded to the identity and clinical characteristics of the subjects. The accuracy, reproducibility, and low interobserver error for this measurement have been demonstrated previously,[283] which we have also achieved in our previous experiments (a mean relative difference of 3% in FMD over time).[284]

FMD and nitroglycerin-induced endothelium-independent vasodilation (NMD) were defined as the percentage increase in vessel diameter after the corresponding stimulation, with reference to baseline. Hyperemia was

calculated as the percentage increase in blood flow after cuff deflation compared with baseline.

7.2.5 Statistical Analysis

Mean (standard deviation), median (interquartile range) and number (percentage) are presented for parametric, non-parametric and categorical data, respectively. Comparisons between controls, PS group and OSA group were made by one-way analysis of variance (ANOVA), Kruskal-Wallis test and χ^2 test for parametric, non-parametric and categorical data, respectively. Bonferroini tests, Mann-Whitney tests and multiple χ^2 tests with adjusted p values (significant at $p<.016$) were used for corresponding post hoc pairwise comparisons. Multiple linear regression analyses were used to assess the main correlates of FMD after adjustment for possible confounding factors. All the statistical analyses were performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois), and a p value <0.05 was considered statistically significant.

7.3 RESULTS

A total of 243 non-obese children and adolescents participated in this study (mean age 10.5±2.8 years; 150 (61.7%) boys; mean BMI z-score 0.32±0.88). FMD and NMD measurements were successfully conducted in all subjects without causing any adverse events. The group comparisons are shown in Table 7.1. Subjects with OSA and PS were younger than controls and

the proportions of boys increased across the SDB severity groups. OSA cases had significantly higher BMI z-score than controls. As was expected, significant higher OAHI, ODI and ArI as well as lower SpO_2 nadir were only found in OSA group rather than PS group compared to controls. There was no significant difference demonstrated in the resting brachial artery diameter between the three groups. PS cases had significantly lower FMD and hyperemia than controls.

Table 7.1 Comparisons between SDB severity groups in non-obese subjects

	Controls (n=59)	PS (n=64)	OSA (n=120)	*p* value
Age (y)[a,b]	11.4 (10.1-13.1)	10.4 (8.3-12.7)	9.5 (7.8-11.1)	<.001
Male gender (%)[b]	45.8	56.2	72.5	<.001
BMI z-score[b]	0.22 (-0.32-0.74)	0.41 (-0.26-0.88)	0.58 (-0.13-1.11)	.036
OAHI (/h)[b,c]	0.20 (0-0.50)	0.34 (0.10-0.64)	5.32 (2.58-14.46)	<.001
SpO_2 nadir (%)[b,c]	95 (93-96)	95 (94-96)	91 (86-93)	<.001
ODI (/h)[b,c]	0 (0-0.3)	0.1 (0-0.5)	0.5 (0.3-1.6)	<.001
ArI[b,c]	9.7 (7.2-13.2)	9.9 (7.8-14.6)	17.0 (11.6-24.2)	<.001
D_{BA} (mm)	2.5 (0.4)	2.5 (0.4)	2.5 (0.3)	.932
FMD (%)[a]	8.4 (1.0)	7.9 (1.3)	8.1 (1.1)	.034
NMD (%)	22.9 (2.3)	22.1 (2.0)	21.9 (2.4)	.818
Hyperemia (%)[a,b]	597 (160)	515 (126)	533 (145)	.005

BMI=body mass index; OAHI=obstructive apnea hypopnea index; ArI=arousal index; D_{BA} = baseline brachial artery diameter; FMD = flow-mediated vasodilation; NMD = nitroglycerin-mediated vasodilation.
[a] significant difference between controls and PS
[b] significant difference between controls and OSA
[c] significant difference between PS and OSA

Multivariate linear regression analyses showed that after adjusting for age, gender, BMI z-score, resting brachial artery diameter and hyperemia, FMD remained significantly lower in the PS group than controls (*p*=0.019), while no significant difference in FMD was found between PS group and OSA group (*p*=0.632) (Table 7.2).

Table 7.2 Multiple linear regression analysis for flow-mediated vasodilation (FMD) as the dependent variable

	β	Standard error	*p* value
PS vs controls	-0.521	0.220	.019
Age	-0.012	0.059	.834
Gender	-0.045	0.245	.855
BMI z-score	0.125	0.128	.330
Vessel diameter	-0.630	0.472	.184
Hyperemia	1.21×10^{-4}	0.001	.872
OSA vs PS	0.090	0.182	.623
Age	0.080	0.049	.105
Gender	0.147	0.195	.453
BMI z-score	0.201	0.105	.058
Vessel diameter	-1.323	0.411	.002
Hyperemia	0.002	0.001	.012

7.4 DISCUSSIONS

In this study, endothelial function was investigated across the SDB spectrum, i.e. from PS to OSA in non-obese children and adolescents. We found that subjects with PS had reduced FMD compared to non-snoring controls after controlling for possible confounding factors, while there was no significant difference in FMD between PS and subjects with OSA.

Increasing number of studies has been published on endothelial function in SDB over the past ten years, whereas almost all of the existing literature focused on patients with OSA. In adults, accumulating evidence indicated that FMD was negatively correlated with OSA severity and could be reversed by CPAP treatment.[275-277] In children, very limited data could be found on

investigating OSA-related endothelial dysfunction (Table 7.3). OSA children showed blunted reperfusion kinetics after release of occlusion compared to non-snoring controls.[278, 280-282] There seemed to be an upward trend in Tmax with increase in OSA severity, although statistical significance was not reached.[279, 281, 282] If only OSA cases and non-snoring controls were analysed in this study, we similarly found that ln OAHI (β=-0.123, standard error=0.047, *p*=.009) and ln ODI (β=-0.381, standard error=0.165, *p*=.023) were associated with FMD. A small intervention study suggested that such endothelial dysfunction was reversible after adenotonsillectomy in OSA cases, especially those who without family history of cardiovascular diseases.[278] Furthermore levels of certain inflammatory biomarkers related to cardiovascular morbidities within the microvasculature such as myeloid-related protein 8/14,[279, 282] platelet-derived microparticles[281] and soluble CD40 ligand[278] were shown to be correlated with endothelial function.

In contrast, only our research group reported PS, the mild end of SDB severity continuum, was also associated with reduced FMD compared to non-snoring controls, independent of age, gender, BMI z-score, resting brachial artery diameter and hyperemia in both normal weight and overweight children.[174] This current study focused on non-obese children and included subjects with OSA as well. Similarly, such endothelial dysfunction associated with PS was verified again. Surprisingly FMD did not exhibit a linear dose-effect relationship across SDB severity spectrum, i.e. FMD in OSA group was not significantly different from that in PS group.

Table 7.3 Published studies on endothelial function in children with SDB

Authors	Subjects	Results
Kim J et al[281]	14 moderate to severe OSA, 65 mild OSA and 56 non-snoring controls; 4-12 years	Peak hyperemic response time in moderate to severe OSA group (44.9±22.3s) and mild OSA group (37.7±18.8s) were longer than that in controls (36.8±21.1s), but did not reach statistical significance.
Kim J et al[282]	34 moderate to severe OSA, 106 mild OSA and 115 non-snoring controls; 5-10 years	Peak hyperemic response time in moderate to severe OSA group (41.9±24.4s) and mild OSA group (36.6±19.6s) were longer than that in controls (36.8±21.1s), but did not reach statistical significance.
Bhattacharjee R et al[279]	54 OSA and 54 non-snoring controls; 4-12 years	In non-obese children, Tmax in controls, mild OSA group and moderate to severe OSA group increased from 24.5±1.3s, 34.8±3.7s to 43.8±14.2s. In obese children, Tmax in controls, mild OSA group and moderate to severe OSA group increased from 40.6±2.9s, 47.1±4.5s to 60.1±5.6s.

(Continued) Published studies on endothelial function in children with SDB

Authors	Subjects	Results
Dubern B et al[285]	51 children with severe obesity	Glyceryl trinitrate-mediated dilation (GTNMD) and incremental elastic modulus (Einc) were significantly correlated with desaturation index (DI) (beta=0.4 and beta=0.27, respectively).
Kheirandish-Gozal et al[280]	80 OSA and 20 non-snoring controls; 4-12 years	OSA group had significantly longer time to peak flow (Tmax) than controls (42.9±9.7s vs 30.1±4.7s). However Tmax was not correlated with apnoea hypopnea index (AHI).
Gozal D et al[278]	26 non-obese prepubertal OSA children and 8 matched controls; 6-11 years	Time required to resume baseline regional blood flow before cuff occlusion was significantly slower in OSA group compared to controls (113±11.4s vs 69.1±9.76s). Such altered endothelial function was reversible 4 to 6 months after adenotonsillectomy, particularly if a family history of cardiovascular disease was not present.
Li et al[174]	73 primary snorers and 128 non-habitual snoring controls; 6-18 years	Normal weight (7.9±1.3 vs 8.5±0.9) and overweight subjects (7.4±1.4 vs 8.1±1.1) with PS had significantly reduced flow-mediated vasodilation (FMD) than controls.

The mechanisms of endothelial function in OSA have been reviewed before. Repetitive episodes of hypoxia/reoxygenation associated with transient cessation of breathing during sleep in OSA resemble ischemia/reperfusion injury and may be the main culprit underlying endothelial dysfunction in OSA. Additional factors such as repetitive arousals resulting in sleep fragmentation contribute to impairment of endothelial function.[271, 272] However it is unknown why endothelial dysfunction would also be present in children with PS. From our data, children with PS had comparable ODI, SpO_2 nadir and ArI with non-snoring children. A possible mechanism may involve the direct effect of snoring itself. A recent animal study showed that carotid arteries subjected to 6 hours of continuous peri-carotid tissue vibration displayed endothelial dysfunction. A reduction in tissue cyclic guanosine monophosphate (cGMP) acetylcholine (Ach) was found in vibrated carotid arteries. ACh induces vasorelaxation via activation of endothelial nitric oxide synthase (eNOS) which in turn generates nitric oxide resulting in vasorelaxation.[24] Whether such mechanisms are also applicable to systemic endothelial dysfunction needs to be further studied. Another possible mechanism is that there were subtle differences between the two groups that could not be detected using the conventional PSG protocol. Hence advanced technologies which may be more sensitive to detect hypoxia and arousal such as EEG spectral analysis, peripheral arterial tonometry and pulse transit time[264, 265] are needed.

On the other hand, the reason why endothelial function between primary snorers and OSA children was similar is hard to explain, since the latter had

more significant hypoxia and arousals than the former. However these two groups both had habitual snoring and we assume that snoring may play a more important role in leading to endothelial dysfunction than hypoxia or sleep fragmentation does, via the possible mechanisms discussed above. This finding suggests that primary snorers probably run similar risk of developing endothelial dysfunction as OSA cases do. Future studies are in need to verify our hypothesis. Another explanation is that we might have misclassified some upper airway resistance syndrome (UARS) cases as PS, as we did not use oesophageal pressure monitoring in our routine monitoring. However a nasal pressure sensor was utilized as a widely accepted alternative method.[222] Although we did not exclusively calculate RERA events, the overall arousal index was not significantly different between our PS and normal control subjects.

Childhood OSA is associated with a number of cardiovascular complications including both remodeling and dysfunction,[142-146] blood pressure elevation,[151, 152, 251, 252] and impairment of autonomic cardiac modulation.[266-268] In recent years, accumulating evidence suggests that childhood PS is also associated with similar morbidities.[173, 175] Studies in adult population showed that impaired FMD was associated with a higher rate of future adverse cardiovascular events.[270] Although longitudinal studies investigating the clinical significance of impaired FMD in children and adolescents are insufficient, existing evidence showed that reduced brachial FMD is present in children with cardiovascular risk factors including obesity[286] and dyslipidemia.[269] Although ABP was not demonstrated to be affected in children with snoring in our cross-

sectional study (Chapter 6), it is reasonable to extrapolate that cardiovascular health in children with PS will be affected if impaired FMD is not reversed in the long run. Therefore PS even in non-obese children should not be considered a completely benign entity.

There were certain limitations to our study. First, our control group was recruited from clinics which may involve selection bias. While the inclusion criteria of controls were relatively stringent, i.e. never snored or only snored less than once per month as well as OAHI<1 confirmed by PSG, which should be able to identify genuine healthy individuals. Second, only a single night PSG was performed and that might misdiagnose some OSA cases as having PS. Our previous study however, demonstrated that single night PSG in children was able to correctly identify 85% of OSA cases, and those missed cases had only borderline OSA.[242] Third, snoring relied on parental report rather than objective assessment. Parents might underestimate the frequency of snoring of their children if they did not sleep in the same bedroom. As a result, some children could have been mislabeled as controls. However, this would have caused under rather than overestimation of the effect of PS on endothelial function.

In conclusion, FMD was lower in PS compared to non-snoring controls and remained similar when SDB severity increasing to OSA in non-obese children and adolescents. Thereby PS can not be regarded as completely benign as it may be linked with long-term cardiovascular morbidities.

CHAPTER 8

Natural History of Primary Snoring in School-aged Children: A 4-Year Follow-up Study

8.1 INTRODUCTION

Snoring is a common symptom of paediatric sleep-disordered breathing (SDB), and the reported prevalence of habitual snoring ranges from 4.0% to 34.5%.[26, 38, 46, 85] SDB includes a spectrum of diseases with severity ranging from primary snoring (PS), upper airway resistance syndrome (UARS) to obstructive sleep apnoea (OSA).[90, 91] In contrast to OSA, PS which is defined as snoring without apnoea, frequent arousals or gas exchange abnormalities[170] has been positioned at the milder end of the SDB severity continuum, [177] and treatment is usually not prescribed.[178]

Nevertheless, whether deferment of treatment for PS is safe has aroused more research recently. Kwok et al found that children with PS had increased casual daytime blood pressure and reduced arterial distensibility.[173] Our research group demonstrated that nighttime blood pressure was also elevated and endothelial function was impaired in children with PS.[174, 175] A more recent study found that PS was a risk factor for hyperactive and inattentive behavior and poor school performance in children.[186] Accumulating evidence suggests PS may be associated with a variety of clinical sequelae, and therefore it should no longer be considered as completely benign.[179]

Another important issue that relates to whether PS if left untreated progresses to OSA, persists or resolves over time is still poorly defined. To our knowledge, only three research studies that examined the natural history of PS in children have been published. The three studies repeated polysomnography (PSG) in cohorts of 20, 9 and 31 children with PS over a 2-year, 3-year and 6-month period respectively. All three studies concluded that PS in children generally did not evolve to OSA over time.[176, 187, 188] These studies, however, had small sample size and consisted of hospital-based subjects.

In this study, we aimed to determine (1) the natural history of PS in school-aged children recruited from the community over a 4-year period and (2) clinical symptoms and risk factors predictive of PS progression to OSA.

8.2 METHODS

8.2.1 Subjects

This was a prospective study of a cohort established between 2003 and 2005 for a childhood OSA epidemiologic study.[94] Children aged 6-13 years from 13 primary schools were randomly recruited. A total of 619 subjects underwent PSG, and 161 were defined as PS (see later discussion in the section of 'Polysomnography' for definition). For this follow-up study, as a result of limited resources, only the first 99 consecutive subjects with PS were invited to undergo repeat assessment. Subjects were excluded from the study if they had cardiovascular, renal or neuromuscular diseases, chromosomal abnormalities, acute illness within two weeks of PSG, or if they had undergone

upper airway surgery or started on continuous positive airway pressure treatment during the follow-up period. Written informed consent and assent were obtained from the parents and subjects respectively. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (CRE_2007.363).

8.2.2 Sleep symptom questionnaire

A validated sleep symptom questionnaire[93] (Appendix 7) was completed by parents of recruited subjects at baseline and follow-up, and the following information was extracted: (1) snoring frequency and other sleep-related symptoms rated on a 6-point scale: 0=never; 1=less than one night per month; 2=one to two nights per month; 3=one to two nights per week; 4=three nights or more per week; 5=unclear. Snoring and other OSA-related symptoms were defined as present if their frequency scored 2-4. (2) Clinical features: history of allergic rhinitis and asthma. (3) Socioeconomic and environmental factors. We defined 'persistent' as having positive history at both time-points.

8.2.3 Anthropometry assessment

The weight, height and Tanner stage of all subjects were assessed on the day of PSG. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Weight, height and BMI were converted to z-scores appropriate for age and gender,according to local reference.[193] Overweight and obese children were defined as a BMI z-score ≥ 1.036 and 1.645, corresponding to the 85th and

95th percentile, respectively. We defined ‘persistent overweight/obesity’ as being overweight or obese at both baseline and follow-up. Pubertal stage was evaluated using a self-assessment questionnaire to categorize Tanner stages.[287] Prepubertal was defined as Tanner stage 1, and pubertal defined as Tanner stage 2 or greater.

8.2.4 Tonsil and adenoid size assessment

The examination was carried out in the morning after overnight PSG by an otorhinolaryngologist. The size of tonsils and adenoids were evaluated by a 4mm rigid rhinoscope (Storz endoscopy, Tuttingen, Germany) and a flexible laryngoscope (P4, Olympus) respectively. The size of tonsils and adenoids was reported as a percentage of the oropharyngeal and nasopharyngeal airway respectively. A large tonsil or adenoid was defined as the soft tissue occupying ≥50% of the corresponding airway. Tonsils and adenoids were further classified as ‘persistently large’ if they were large at both time-points.

8.2.5 Polysomnography (PSG)

All recruited children underwent initial and follow-up standard overnight PSG at a dedicated sleep laboratory with CNS 1000P polygraph (CNS Inc, Chanhassen, Minnesota, USA). In brief, the central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram and electrocardiogram were recorded. The positions of the subject, respiratory airflow (oro-nasal thermal sensor and nasal

cannula connected to air pressure transducer), respiratory effortswork of breathing (chest and abdominal wall motion connected to piezoelectric transducer), arterial oxyhaemoglobin saturation with a signal averaging time of three seconds (SpO2, by Ohmeda 3700 pulse oximeter, Boulder, CO, USA) were measured. All data were scored by experienced PSG technologists. At baseline standard criteria described in our previous publication was used for scoring.[243] While at follow-up, the new AASM 2007 paediatric polysomnography scoring criteria was used.[222] Therefore all the baseline data of PS subjects who participated in our follow-up study was rescored using AASM criteria. Those who were not classified as PS by the new criteria were excluded.

Obstructive apnoea hypopnea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation >3% per hour of sleep. The oxygen saturation nadir (SpO_2 nadir) was also noted. Arousal index (ArI) was defined as the total number of arousals per hour of sleep.

Children who snored were diagnosed to have PS if their OAHI<1 and SpO_2 nadir≥90%. At follow-up, children were diagnosed to have OSA if their OAHI≥1. Normal subjects were defined as non-snorers with OAHI<1 and SpO_2 nadir≥90%.

8.2.6 Statistical Analysis

Student t tests, Mann-Whitney U tests and chi square tests were used to detect difference between subjects who participated in this study and those who did not for parametric, non-parametric and categorical data respectively. Paired t tests, Wilcoxon signed rank tests and McNemar tests were used to examine intra-group differences between baseline and follow-up for parametric, non-parametric and categorical data respectively. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio together with their 95%CI of OSA-related symptoms were calculated using an online software http://vassarstats.net/clin1.html. Binary logistic regression analyses were performed to investigate factors associated with progression of PS to OSA and resolution of PS to normal at follow-up seperately. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois), and a p value <0.05 was considered statistically significant.

8.3 RESULTS

Of the 99 subjects invited, we failed to contact 6 and 18 refused to participate. One case who had received tonsillectomy for recurrent tonsillitis during the follow-up period was excluded. Therefore 74 subjects with PS participated in this follow-up study. There were no significant differences in demographic, clinical, environmental, socioeconomic or polysomnographic characteristics between the 74 who participated and the 87 who did not (Table 8.1). Four participants had OAHI≥1 at baseline using AASM 2007 criteria during

rescoring, so a total of 70 subjects were included for final analysis. Mean time of reevaluation was 4.6±0.6 (range 3.4-6.2) years after the initial assessment.

Table 8.1. Characteristics of children with PS who did and did not participate in the follow-up study

	Participants (n=74)	Non-participants (n=87)	*p* value
Age (years)	10.1(1.7)	10.3(1.7)	.52
Male gender (n,(%))	50 (67.6)	55 (63.2)	.56
Weight (kg)	34.5 (9.7)	35.2 (10.4)	.65
Height (cm)	137 (11.2)	139 (11.2)	.25
BMI (kg/m^2)	18.0 (3.1)	17.9 (3.3)	.74
BMI z-score	0.47 (0.95)	0.38 (1.08)	.52
Puberty (n,(%))	13 (17.6)	17 (19.5)	.75
Large tonsils (n,(%))	7 (9.5)	13 (14.9)	.29
Large adenoids (n,(%))	3 (4.1)	6 (6.9)	.43
Snoring (n,(%))			.52
Sometimes	19 (25.7)	20 (23.5)	
Often	30 (40.5)	30 (34.5)	
Frequently	25 (33.8)	37 (42.5)	
Allergic rhinitis (n,(%))	62 (83.8)	67 (77.0)	.28
Asthma (n,(%))	11 (14.9)	9 (10.3)	.39
Household smoking (n,(%))	16 (21.6)	28 (32.2)	.13
Share bedroom with others (n,(%))	58 (78.4)	62 (71.3)	.30
Family income (n,(%))			.09
≤HK$10,000	14 (18.9)	29 (33.3)	
HK$10,001-20,000	45 (60.8)	47 (54.0)	
>HK$20,000	15 (20.3)	11 (12.6)	
Paternal education (n,(%))			.58
Primary or below	7 (9.5)	13 (14.9)	
Secondary	56 (75.7)	62 (71.3)	
Tertiary or above	11 (14.9)	12 (13.8)	
Maternal education (n,(%))			.81
Primary or below	9 (12.2)	10 (11.5)	
Secondary	55 (74.3)	68 (78.2)	
Tertiary or above	10 (13.5)	9 (10.3)	
OAHI (/hr)	0.12 (0.00-0.46)	0.15 (0.00-0.50)	.63
SpO_2 nadir (%)	93 (92-95)	93 (92-94)	.67

Mean (SD), median (IQR) and number (%) are presented for parametric, non-parametric and categorical data, respectively.
BMI: body mass index; OAHI: obstructive apnoea hypopnoea index; SpO_2 nadir: oxygen saturation nadir.

8.3.1 Subjects' characteristics at baseline and follow-up

For the whole group, changes in anthropometric and PSG parameters over the follow-up period are shown in Table 2. As expected, subjects had significant increase in weight and height however their average BMI z-score remained unchanged. The proportion of pubertal children increased from 12.9% to 100%. Only six subjects had large tonsils at baseline, of whom 3 had persistently large tonsils at follow-up. Three subjects had large adenoids at baseline but none at follow-up. None of the subjects had new onset of large tonsils or adenoids at follow-up. OAHI, ArI and ODI increased while SpO_2 nadir decreased significantly over the follow-up period (Figure 8.1 and Table 8.2).

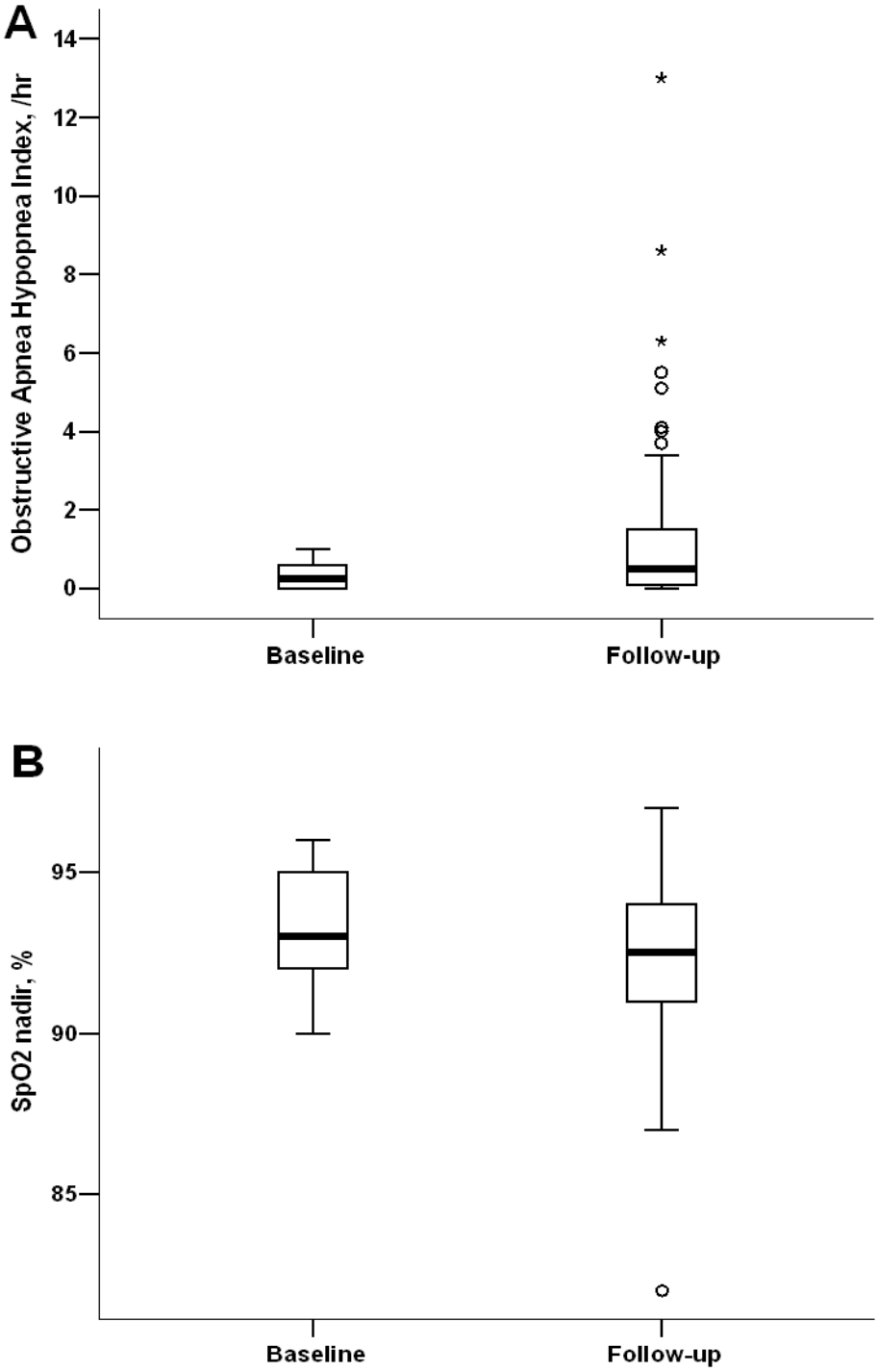
Twenty-six of the 70 subjects (37.1%) developed OSA at follow-up. Their median OAHI was 2.05 (ranging from 1.00 to 13.01), and 5 subjects (7.1%) had OAHI≥5. Amongst the remaining subjects without OSA at follow-up, 22 (31.4%) remained as PS and 18 (25.7%) became normal. Four subjects were unclassified at follow-up, of whom 2 had OAHI<1 but unclear snoring status and 2 had OAHI<1 but their SpO_2 nadir <90%.

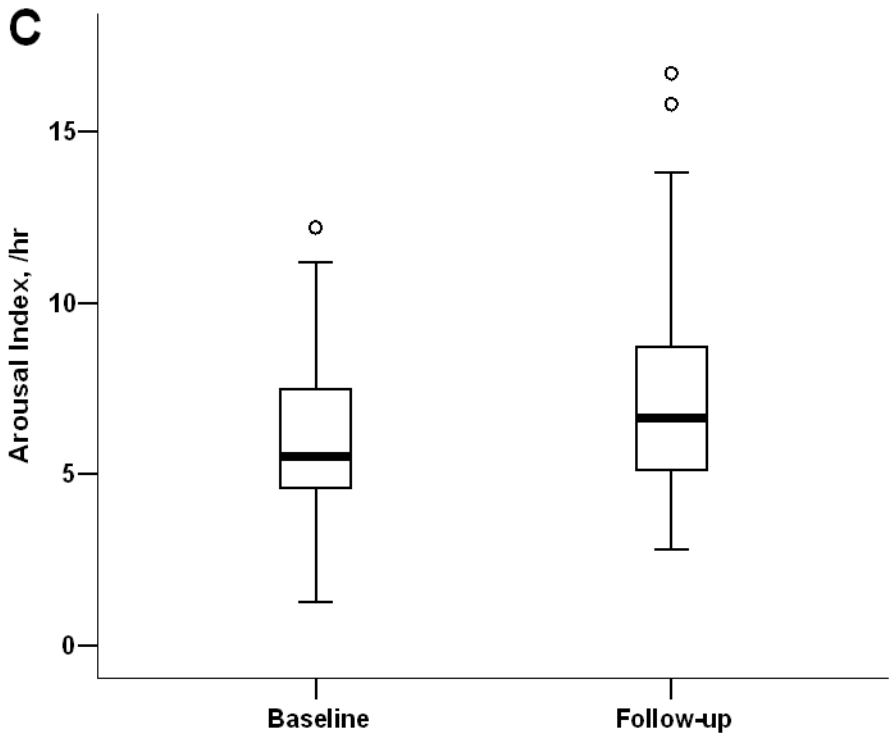
Table 8.2 Anthropometric and polysomnographic data of the subjects (n=70) at baseline and follow-up

	Baseline	Follow-up	*p* value
Age (year)	10.2 (1.7)	14.7 (1.8)	<.001
Weight (kg)	35.0 (9.7)	55.7 (13.2)	<.001
Weight z-score	0.36 (0.96)	0.59 (1.02)	<.01
Height (cm)	138 (11.5)	162 (8.8)	<.001
Height z-score	-0.02 (1.11)	0.35 (1.27)	.01
BMI (kg/m^2)	18.2 (3.1)	21.1 (3.9)	<.001
BMI z-score	0.50 (0.94)	0.53 (0.90)	.68
Tanner stage (n,(%))			<.001
Tanner 1	61 (87.1)	0 (0)	
Tanner 2	5 (7.1)	9 (12.9)	
Tanner 3	3 (4.3)	25 (35.7)	
Tanner 4	1 (1.4)	32 (45.7)	
Tanner 5	0 (0)	4 (5.7)	
Large tonsils (n,(%))	6 (8.6)	3 (4.3)	.49
Large adenoids (n,(%))	3 (4.3)	0 (0)	.25
Sleep efficiency (%)	86.0 (77.4-89.2)	87.0 (77.0-92.2)	.54
Sleep latency (min)	15 (8-24)	12 (9-17)	.01
REM latency (min)	132 (96-168)	93 (75-171)	.13
Stage N1 (% TST)	7.1 (2.8)	8.5 (3.9)	<.01
Stage N2 (% TST)	46.2 (6.2)	48.7 (6.0)	<.01
SWS (% TST)	25.1 (5.8)	21.4 (6.4)	<.001
REM (% TST)	20.2 (4.3)	21.4 (4.1)	.04
OAHI (/hr)	0.25 (0-0.61)	0.50 (0.08-1.50)	<.001
SpO_2 nadir (%)	93 (92-95)	93 (91-94)	.04
ArI (/hr)	5.5 (4.6-7.5)	6.7 (5.1-8.7)	.03
ODI (/hr)	0.12 (0-0.35)	0.19 (0-0.59)	<.01

Mean (SD), median (IQR) and number (%) are presented for parametric, non-parametric and categorical data, respectively.
BMI, body mass index; REM, rapid eye movement; TST, total sleep time; SWS, slow wave sleep; OAHI, obstructive apnoea hypopnoea index; SpO_2 nadir, oxygen saturation nadir; ArI, arousal index; ODI, oxygen desaturation index.

Figure 8.1. Change in (A) obstructive apnoea hypopnea index, (B) SpO2 nadir, (C) arousal index and (D) oxygen desaturation index of the subject over the follow-up period




C
Arousal Index, /hr
15
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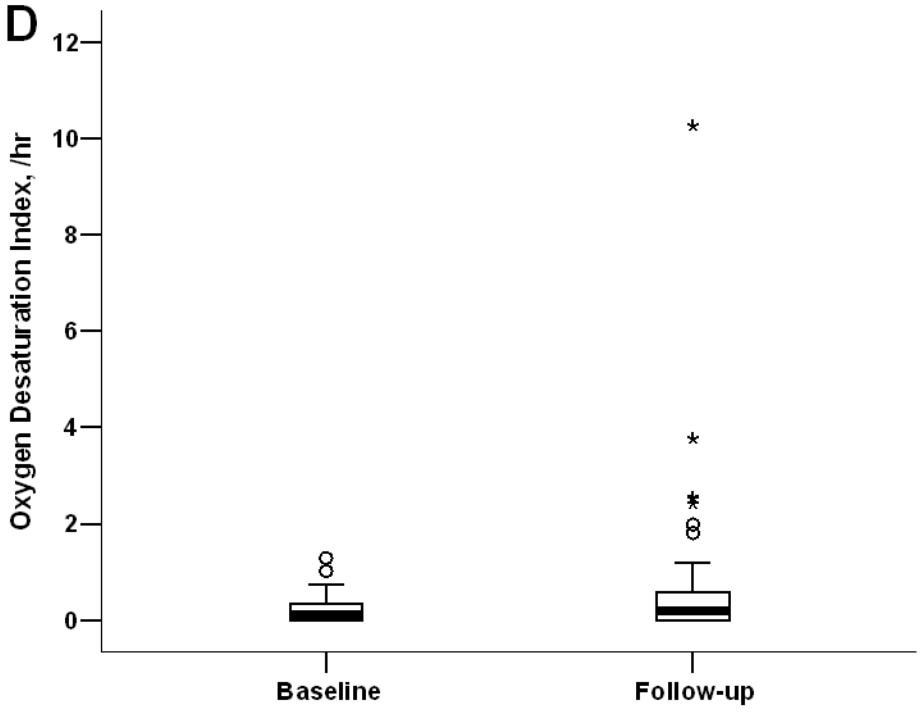
Baseline
Follow-up


D
Oxygen Desaturation Index, /hr
12
10
8
6
4
2
0
Baseline
Follow-up

8.3.2 Predictive clinical symptoms and risk factors for PS progression to OSA

Among the OSA-related clinical symptoms, only persistent snoring was significantly different between those who did and did not develop OSA at follow-up (p=0.007). Persistent snoring had a relatively high sensitivity (87.5%, 95%CI 66.5%-96.7%) and negative predictive value (NPV) (86.4%, 95%CI 64.0%-96.4%) despite poor specificity (45.2%, 95%CI 30.2%-61.2%) and positive predictive value (PPV) (47.7%, 95%CI 32.7%-63.1%) for the development of OSA. The positive likelihood ratio and negative likelihood ratio of persistent snoring was 1.60 (95%CI 1.17-2.19) and 0.28 (0.09-0.84) respectively for the development of OSA.

We analysed the effects of several potential factors in predicting progression, persistence or resolution of PS using logistic regression models (Table 8.3). In identifying the risk factors for worsening of PS, the univariate analysis showed only the presence of persistent overweight/obesity was significantly associated with progression to OSA, with odds ratio of 7.33 (95% CI=1.41-38.13). In a multivariate model adjusted for baseline age, gender, persistently large tonsils and persistent snoring, the presence of persistent overweight/obesity remained the only significant predictor, with odds ratio of 7.95 (95% CI=1.43-44.09). In contrast, no factors were found to be significantly associated with remission of PS.

Table 8.3. Logistic regression analysis assessing the potential factors associated with the worsening or remission of PS

	PS at follow-up vs OSA at follow-up		PS at follow-up vs normal at follow-up	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Male gender	2.25 (0.69-7.32)	—	0.64 (0.18-2.25)	—
Baseline variables				
Age	0.91 (0.65-1.29)	—	0.76 (0.50-1.15)	—
BMI z-score	1.40 (0.75-2.64)		1.18 (0.59-2.36)	
Overweight/obesity	3.40 (0.97-11.98)		0.77 (0.18-3.21)	
Tanner stage	0.46 (0.11-1.90)		0.73 (0.30-3.21)	
Large tonsils	2.74 (0.26-28.41)		0.38 (0.03-4.58)	
Large adenoids	—		—	
Allergic rhinitis	0.43 (0.10-1.91)		0.37 (0.04-3.93)	
Asthma	0.38 (0.06-2.28)		1.18 (0.29-11.04)	

(Continued) Logistic regression analysis assessing the potential factors associated with the worsening or remission of PS

	PS at follow-up vs OSA at follow-up		PS at follow-up vs normal at follow-up	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Change over follow-up period				
Change in BMI z-score	1.00 (0.41-2.43)		1.40 (0.54-3.59)	
Persistent overweight/obesity	7.33 (1.41-38.13)	7.95† (1.43-44.09)	0.80 (0.10-6.32)	— §
Persistent non-overweight/ obesity	0.71 (0.23-2.23)		0.60 (0.17-2.18)	
Persistently large tonsils	—	—	—	—
Persistent snoring	—	—		

†Adjusted for baseline age, gender, persistently large tonsils and persistent snoring. § Adjusted for baseline age, gender and persistently large tonsils. — Without significance.

8.4 DISCUSSIONS

In this community-based follow-up study of children with PS, we demonstrated that more than one third of the subjects progressed to OSA over a period of 4 years. Persistent snoring had a relatively high NPV for PS progression. Persistent overweight/obesity placed children with PS at an increased risk for such progression. To our knowledge, this study on the natural history of PS in children is the first to report a significant proportion of subjects with disease progression to OSA and its associated risk factors.

Studies examining natural history of PS are scarce in both adults and children. The comparison between our study and the other three published paediatric studies is shown in Table 8.4. None of the previous studies found

significant changes in respiratory parameters for the group as a whole, and the proportion of subjects progressed to OSA was much lower than in our study.[176, 187, 188] One possible explanation for this discrepancy is our longer follow-up period, which would allow subjects greater exposure time to risk factor(s) leading to disease progression. One such risk factor was persistent overweight/obesity. This is understandable as obesity is a well-established risk factor for OSA.[94, 288] Our present study provided robust evidence that obesity is a significant risk factor in causing disease progression along the SDB severity spectrum in children. Therefore weight reduction may play an important role in preventing PS from pregressing to OSA for overweight/obese children. However in our study cohort the overall magnitude of change in BMI z-score was only moderate, and we were unable to demonstrate a significant association between change in BMI z-score and progression of PS. Further intervention study to verify this hypothesis is needed.

The age range in our study was older than the other series. At follow-up all of our subjects had reached puberty. We however, failed to find a significant effect of puberty on PS progression. Previous studies showed that apnoea hypopnea index had no correlation with Tanner stage in healthy adolescents.[226] It has also been suggested that changes in sex hormones were not a primary modulator of upper airway function during transition from childhood to adulthood.[289] Thus the role of puberty in SDB remains undefined at present. On a similar note, we failed to identify gender as a significant risk factor for PS progression in this current study.

There is also discrepancy in the percentage of resolved PS across the four studies (Table 8.4), likely a result of different definitions used for PS resolution. All three published studies only used decreased questionnaire-based symptom scores to define resolution of PS. We however, classified resolution of PS as absence of snoring together with normal PSG findings.

Adenotonsillar hypertrophy was not found to be associated with PS progression in this study. It may be because the mean age of our cohort at baseline and follow-up were both beyond the peak age of lymphoid hypertrophy.[195] This data was however not fully analysed in previous studies where they included younger participants (Table 8.4).

In school-aged children, PS is not necessarily a stable status, especially those who remained overweight or obese. Moreover, presence of persistent snoring can also be used as a guide for disease progression. Persistent snoring has a relatively high NPV for development of OSA, meaning that if a child with PS did not continue to snore it was less likely that he/she would develop OSA. Thus a clinician could give priority for repeat assessment for children with PS who remain overweight or obese and/or with persistent snoring. Randomized controlled studies are needed to assess whether obese children with PS can be prevented from progressing to the development of OSA with weight reduction.

There were a few limitations in this study. Firstly, oesophageal pressure monitoring was not used thus cases with UARS would have been missed. Nevertheless nasal pressure was monitored in our study, which made up for this potential source of error to some extent. Moreover, we compared baseline

arousal index of normal healthy subjects from our previous epidemiologic study with that of the 74 PS subjects in this study, and no significant differences were found. Secondly, other potential factors associated with progression or resolution of PS such as change in craniofacial structure or fat deposition in the upper airway were not performed in this study.

In summary, more than one third of children with PS progressed over a 4-year period to develop OSA, and persistent overweight/obesity was a significant risk factor. Therefore in the management of school-aged children with PS, great attention should be paid to weight control. As accumulating evidence suggest PS is also associated with important sequelae, further studies should examine the potential beneficial effects of intervention for this common paediatric problem.

Table 8.4. Comparison of our findings and previous studies on natural history of PS in children

	Li et al	Marcus et al	Topol et al	Nieminen et al
Number of PS subjects who underwent repeat PSG	70	20	9	31
Mean Age at initial assessment (year)	10.2±1.7	6±4	7.2±2.4	6.0±1.8
Male gender (n,(%))	42(60.0)	12(60)	5(55.5)	17(54.8)
Mean Follow-up period	4.6 years	2 years	3.2 years	6 months
Baseline BMI	18.2±3.1	17.6±4.3	NA	NA
Change in BMI z-score	Not significant	Not significant[(1)]	NA	NA
Change in PSG parameters	Significant	Not significant	Not significant	Not significant
Progression to OSA (n,(%))	26(37.1)	2(10)	1(11.1)	1(3.2)
Resolution of PS (n,(%))	18(25.7)	2(10)	5(38.4)[(2)]	16(43.2)[(3)]

NA, not available.

(1) Chang in BMI

(2) Thirteen subjects completed sleep questionnaires.

(3) Thirty-seven subjects (31 primary snorers and 6 children with mild OSA) completed sleep questionnaires.

CHAPTER 9

GENERAL CONCLUSIONS

Snoring is a low-frequency sound produced by vibrations of the soft tissues of the oropharyngeal walls during sleep.[189] It represents the most frequent symptom of sleep disordered breathing (SDB), which includes a spectrum of diseases with severity ranging from primary snoring (PS), upper airway resistance syndrome (UARS) to obstructive sleep apnoea (OSA).[91] Childhood OSA has been demonstrated to lead to a large array of clinical complications, including neurocognitive impairments and cardiovascular abnormalities. Childhood PS, defined as snoring without apnoeas, frequent arousals or gas exchange abnormalities is positioned at the mild end of SDB continuum.[170] Primary snoring is usually considered as benign and no treatment needs to be prescribed according to current guidelines.[178]

This thesis examined the prevalence and risk factors of snoring in Chinese children in Hong Kong and investigated whether even childhood PS would be associated with clinical sequelae, disturbance in sleep architecture, and whether PS would progress to OSA if left untreated over a period of time.

Based on our findings, the prevalence rate of habitual snoring (snoring frequency ≥3 nights/week) is 5.5% in preschool children and 9.2% in school-aged children and adolescents, suggesting that habitual snoring is common in the Chinese paediatric population. The prevalence rates of habitual snoring vary widely in different countries and areas, and our reported rates are in the

average range, but slightly low in preschool children. It is likely that inter-ethnic differences may be present in craniofacial morphology and body fat distribution that interact to produce the snoring susceptible phenotype.

The peak age of developing habitual snoring is 6 years in preschoolers. This maybe related to the physiological growth and subsequent regression of adenoids and tonsils. School-aged boys are found to run a higher risk of developing habitual snoring, and this is especially true after entering puberty. Obesity is a significant risk factor for developing habitual snoring, no matter in toddlers or in school-aged children. It is understandable because obesity leads to restricted upper airway size primarily through overgrowth and crowding of soft tissues.[15] Therefore weight reduction is essential in the management of snoring. Allergies causing nasal and upper airway inflammation and blockage might explain that children with allergic diseases and/or family history are prone to having habitual snoring. Hence it is worthy of investigation whether anti-inflammation therapy would be effective in alleviating snoring. Studies showed that nasal corticosteroids helped to reduce frequency of snoring based on parent-reported questionnaire.[20] The more a child is exposed to household smoking, the higher risk he/she will have in developing snoring. The underpinning mechanism is not clear though. Encouraging parents to conduct smoking cessation is a potential way to alleviate childhood snoring. In preschool children habitual snoring is not only a self-existent manifestation but also associated with other sleep problems including going to sleep reluctantly, difficulty in falling asleep, night awakenings, sleep in prone position and overall

poor sleep quality, which further increases the clinical importance of controlling childhood snoring.

As far as neurocognitive complications of childhood PS is concerned, primary school aged boys with snoring have significantly lower IQ scores than non-snoring counterparts, although the mean IQ score is still within normal range. However snoring seems to have no significant effect on girls' neurocognitive function. This finding suggests more attention should be attached to boys' snoring, because it is more likely to associate with impairment in neurocognitive function. However children with PS in our study was not found to have significantly worse neurocognitive performance compared to non-snoring healthy controls. Nevertheless there was a trend towards poorer sustained attention across the SDB severity spectrum increasing from control, PS to OSA, independent of age, gender and parental socioeconomic status. Taking such a small sample size in our study into account, it therefore is inconclusive whether childhood PS is associated with neurocognitive function impairment. The chances are that the trend will become a significant difference with increase in sample size. The possible mechanism of snoring causing neurocognitive dysfunction might include subtle oxygen desaturations and sleep architecture disturbance secondary to micro-arousals. Further studies in this aspect are needed.

In terms of cardiovascular consequences of childhood PS, FMD was lower in PS subjects compared to non-snoring controls and significant difference remained after adjustment for confounding factors including age, gender, BMI z-

score etc. Since endothelial dysfunction is a well-established mechanism mediating cardiovascular morbidities, our result suggests that even childhood PS may have the risk for developing cardiovascular diseases in the future. We also explored the association between snoring and BP, and found that parent-reported questionnaire based habitual snoring is not able to independently predict elevation of ambulatory BP in children.

We subsequently examined whether sleep would be disturbed in primary snorers, i.e. whether their sleep architecture would be affected. We demonstrated that normal sleep architecture was preserved in prepubertal children with PS. Nevertheless pubertal adolescents with PS had increased stage 1 sleep and WASO than non-snoring healthy controls. However clinical relevance related to such disturbance in sleep architecture in PS remains unclear.

Last, we investigated the natural history of childhood PS. More than one third of school-aged children with PS may progress to OSA over a 4-year period, though only <10% may develop moderate-to-severe disease. Persistent overweight/obesity is a significant risk factor for the development of OSA at follow-up. Thus weight control might be an important component in the prevention for worsening of childhood PS.

In conclusion, snoring is commonly present in children and adolescents. Childhood PS is found to be related to endothelial dysfunction, and sleep architecture is altered in pubertal children with PS. Although neurocongitive function is not significantly impaired in childhood PS, a trend towards its

adverse effect exists. Furthermore, if left untreated, over one third of PS subjects may progress to OSA, especially those who are persistently obese or overweight. Therefore childhood PS may not be considered as totally benign any more.

Thus future research should begin to explore ways in dealing with childhood PS. The alternative non-invasive therapy may include weight reduction or anti-inflammation medication such as intranasal corticosteroid spray (ICS), leukotriene receptor antagonist, etc. Change in snoring symptom quantified by an objective snoring sound recorder and PSG indexes may be compared between treatment group and watchful waiting group over a period of follow-up.

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My involvement in this thesis

1. Chapter 2 Prevalence of Snoring in Chinese Preschool Children: data entry, data analysis;
2. Chapter 3 Prevalence of Snoring in Chinese School-aged Children and adolescents: data analysis;
3. Chapter 4 Neurocognitive Functions in School-aged Children with Primary Snoring: PSG interpretation, data analysis;
4. Chapter 5 Sleep Architecture in School-aged Children with Primary Snoring: PSG interpretation, data analysis;
5. Chapter 6 Association between Habitual Snoring and Ambulatory Blood Pressure in Children: data analysis;
6. Chapter 7 Endothelial Function in Children with Primary Snoring: patient recruitment, data collection, PSG interpretation, data entry, data analysis;
7. Chapter 8 Natural History of Primary Snoring in School-aged Chidlren: patient recruitment, data collection, PSG interpretation, data entry, data analysis

Appendix

香港中文大學兒童睡眠調查

學校名稱：_____

學生姓名：_____ Name: _____

性別：男 / 女

年齡：_____

請以你的孩子過去 二個星期 的睡眠狀況回答下列問題。 謝謝。

1. 你的孩子在家中排行第幾？

- ❍ 老大
- ❍ 中間
- ❍ 老么
- ❍ 多胎孩子 (例如：雙胞胎或三胞胎)
- ❍ 獨生子女

2. 你的孩子在睡眠時有否打鼾？

- ❍ 從不
- ❍ 只在他／她患有感冒或過敏時
- ❍ 有時候
- ❍ 常常/經常 → 我的孩子每週打鼾 _____ 次

3. 你的孩子通常在那裡睡覺？

- ❍ 在他／她自己的房間
- ❍ 在父母房間
- ❍ 在兄弟姊妹房間或其它房間
- ❍ 在家中的其它非睡房(如：客廳)
- ❍ 其它, 請列明: _____

4. 你的孩子在睡覺時房間的燈開著還是關掉?

- ❍ 開著
- ❍ 關掉
- ❍ 只有床頭燈或地/牆燈開著
- ❍ 沒有偏愛

5. 你的孩子通常在以下那種寢具睡覺？

- ❍ 小兒床或輕便小床
- ❍ 自己的睡床 (任何大小)
- ❍ 父母的睡床(任何大小)
- ❍ 其它， 請列明: _____

6. 你的孩子睡眠時有否開啟空調？
   - ❍ 有
   - ❍ 沒有
   - ❍ 天氣熱時開啟

7. 通常那種是你的孩子的睡姿？

- ❍ 伏睡
- ❍ 側睡
- ❍ 仰睡

8. 以下那項是你的孩子睡眠前一小時常進行的項目？ (選擇所在進行的項目)

- ❑ 洗澡
- ❑ 按摩
- ❑ 閱讀 / 聽故事
- ❑ 搖抱
- ❑ 看電視
- ❑ 進食晚餐或小吃
- ❑ 喝瓶裝奶或母乳
- ❑ 到處跑
- ❑ 刷牙
- ❑ 玩耍
- ❑ 擁抱
- ❑ 禱告
- ❑ 唱歌
- ❑ 聽音樂
- ❑ 肩扛
- ❑ 其它， 請列明:_____

9. 你的孩子通常是怎樣入睡？(選擇所在進行的項目)

- ❑ 喝瓶裝奶時
- ❑ 喝母乳時
- ❑ 搖抱時
- ❑ 抱著時
- ❑ 看電視時
- ❑ 搖籃或嬰兒推車
- ❑ 在吊床時
- ❑ 獨自睡在房裡的日式床墊或榻榻米時
- ❑ 與父母在房裡的日式床墊或榻榻米時
- ❑ 獨自睡在房裡的嬰兒床時

- ❑ 獨自睡在父母的房裡
- ❑ 與父母在房裡的嬰兒床（任何大小）時
- ❑ 與父親或母親在父母睡房的床
- ❑ 在家中的其它非睡房(如：客廳)
- ❑ 其它， 請列明:_____

10. 一星期七天裡，你的孩子有多少天在睡前所進行的項目是一樣的？

- ❍ 從不
- ❍ 每周 1-2 晚
- ❍ 每周 3-4 晚
- ❍ 每周 5-6 晚
- ❍ 每晚

11. 你通常在甚麼時候開始孩子的睡前晚間項目？_____
例如： 8:00 PM, 8:15 PM, 8:30 PM, 8:45 PM, 9:00 PM, 9:15 PM, 9:30 PM, 9:45 PM, 10:00 PM,

12. 你通常在晚間甚麼時間讓孩子上床？_____
(關燈時間) 8:00 PM, 8:15 PM, 8:30 PM, 8:45 PM, 9:00 PM, 9:15 PM, 9:30 PM, 9:45 PM, 10:00 PM,

13. 一般，你讓孩子上床睡眠有多麼困難，例如，煩擾，哭泣，抗議？

❍	❍	❍	❍	❍
非常容易	有些容易	不容易也不困難	有些困難	非常困難

14. 一般情況下，你的孩子在晚間需要多長時間才能入睡？
例如: 若你讓孩子 8:15 PM 上床睡覺，孩子在 8:30 PM 入睡，即你的孩子需 15 分鐘入睡。
- ❍ 小於 5 分鐘
- ❍ 5-15 分鐘
- ❍ 16-30 分鐘
- ❍ 31-60 分鐘
- ❍ 多於 1 小時

15. 如果你的孩子在晚間有入睡困難，那有多頻繁？

- ❍ 每晚
- ❍ 每周 5 – 6 晚
- ❍ 每周 3 – 4 晚
- ❍ 每周 1 – 2 晚
- ❍ 每月 1 – 3 晚
- ❍ 每月小於 1 次
- ❍ 從不

16. 孩子睡眠時是否需要毛公仔或玩具?

- ❍ 是

- ❍ 否

17. 孩子從不與你同床?

- ❍ 是
- ❍ 否

18. 一般情況下，你的孩子夜間醒來多少次？每晚 _____ 次

19.若你的孩子夜間會醒來，那有多頻繁？

- ❍ 每晚
- ❍ 每周 5 – 6 晚
- ❍ 每周 3 – 4 晚
- ❍ 每周 1 – 2 晚
- ❍ 每月 1 – 3 晚
- ❍ 每月小於 1 次
- ❍ 從不

20. 當你的孩子夜間醒來時，你會怎樣做？(選擇所在進行的項目)

- ❑ 抱起我的孩子並且抱著或者搖抱他/她直到孩子睡著
- ❑ 抱起我的孩子並且在 他/她是醒的時候放回床上
- ❑ 撫摸或輕拍我的孩子，但不會把孩子抱起或帶離睡床
- ❑ 給予瓶裝奶至孩子再睡著
- ❑ 給予母乳讓孩子再入睡
- ❑ 給我的孩子一個奶嘴
- ❑ 換襁褓
- ❑ 用語言安慰我的孩子但不會抱起孩子或帶離睡床
- ❑ 把我的孩子帶到我的床睡
- ❑ 讓我的孩子哭和自行再入睡
- ❑ 觀察我的孩子數分鐘，看他/她能否再入睡
- ❑ 與我的孩子玩耍直至孩子準備再睡覺
- ❑ 與孩子看電視/錄像直至他/她入睡
- ❑ 唱歌給孩子聽
- ❑ 其它， 請列明:_____

21. 當你的孩子夜間醒來時，你會何時作出反應?

- ❍ 立即
- ❍ 5-30 分鐘
- ❍ ½-1 小時
- ❍ 不理會，至他/她自己入睡

22. 一般情況下，你的孩子在夜間睡眠時有多少時間是醒來的？

_____ 小時 _____ 分鐘

例如: 若你的孩子醒來兩次，每次 15 分鐘，那你的孩子醒來的總時間是 30 分鐘。

23. 一般情況下，你的孩子在夜間睡眠持續未有醒來的時段是多少？

_____小時_____分鐘

24.你的孩子在早上甚麼時間睡醒？ _____

例如： 7:00 AM, 7:15 AM, 7:30 AM, 7:45 AM, 8:00 AM,

25. 你的孩子在夜間睡眠的時間多長？(晚上 7 時到早上 8 時)

_____小時 _____分鐘

26. 一般情況下，你的孩子在日間小睡多少次？ (早上 8 時到晚上 7 時)

_____小睡次數

27. 你的孩子在日間的睡眠時間共多少？ (早上 8 時到晚上 7 時)

_____小時_____分鐘

例如: 若你的孩子有兩次小睡，每次 1 小時，你的孩子就在日間睡了兩小時。

28. 請評定你的孩子夜間睡的情況：

❍ ❍ ❍ ❍ ❍ ❍

非常好 好 尚好 較差 差 非常差

若答案是較差、差或非常差，請選擇屬於以下那項問題

- ❍ 入睡困難
- ❍ 經常醒
- ❍ 連續睡眠時間短
- ❍ 其它， 請列明: _____

29. 你是否覺得你的孩子的睡眠是有問題？

- ❍ 非常嚴重的問題
- ❍ 小問題
- ❍ 沒問題

30. 住所類型？

- ❍ 公屋
- ❍ 私人住宅
- ❍ 獨立屋
- ❍ 其它， 請列明: _____

31. 你現在的職業類別是?

- ❍ 全職
- ❍ 兼職
- ❍ 在產假期間
- ❍ 主婦/家長

- ❍ 學生
- ❍ 無業/待業
- ❍ 其它， 請列明: _____

32. 家中有多少位家庭成員?_____ 位

33. 每月家庭總收入大約是(港元)

- ❍ 小於 10,000
- ❍ 1,0000-20,000
- ❍ 20,000-30,000
- ❍ 30,000-40,000
- ❍ 40,000-50,000
- ❍ 50,000-60,000
- ❍ 60,000-70,000
- ❍ 多於 70,000

34. 你的孩子是否因病要定時復診？(除了免疫注射和嬰兒體檢)

- ❍ 是
- ❍ 否

35. 孩子的日間照顧者是誰？

- ❍ 父母 Parent
- ❍ 祖父母 Grandparent
- ❍ 其他親戚 Other relative
- ❍ 其他照顧者(例如：傭人，保姆)
- ❍ 專業日間照顧服務
- ❍ 其它， 請列明: _____

多謝你的參與！

學 童 健 康 調 查 問 卷 2009

在這份問卷中，**"孩子"**是指將問卷從學校帶回家中的孩子。
請按指示回答問題，並在適當的方格加上 √ 或填上答案。

---

1. 請問這份問卷由誰人作答？

孩子的父親 ☐1　　孩子的母親 ☐2　　其他 ☐3

9

2. 填寫問卷的日期： 2009 年 ☐☐ 月 ☐☐ 日

1-12　　1-31　　99

3. 孩子的姓名： ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

must not be missing

4. 孩子就讀的學校： ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

must not be missing

5. 孩子就讀的班級： ☐☐

11-49　　99

6. 你們的地址： ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1-18　　99

7. 住址電話： ☐☐☐☐☐☐☐☐
父親手提電話： ☐☐☐☐☐☐☐☐
母親手提電話： ☐☐☐☐☐☐☐☐

99999999

8. 孩子是： 華人 ☐1　　非華人 ☐2　　9

↓

請註明： ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

char 50　　NO

9. 孩子是男孩或女孩？

男 ☐1
女 ☐2 9

10. 孩子在何時出生？ ☐ 年 ☐ 月 ☐ 日
2001-2007 1-12 1-31 9999/99

11. 孩子的年齡是： ☐ 歲
0-7 99

12. 孩子是否在香港出生？

是 ☐1
否 ☐2 → 9

請註明地點：☐
char 50 NO

請註明孩子遷往香港時的年齡：

年齡： ☐ 歲 ☐ 個月
0-7 99 0-12 99

（若孩子在 1 歲 10 個月大時遷往香港，就應在方格填上 1 歲 10 個月。）

13. 孩子是否經自然分娩出世？

是 ☐1
否 ☐2 → 9

請註明分娩孩子的方法：

經鉗取出 ☐1
經真空吸出 ☐2
經剖腹〔開刀〕取出 ☐3 9

14. 孩子的母親是否在香港出生？

是 ☐1
否 ☐2 → 請註明地點：☐
9 char 50 NO

15. 孩子的父親是否在香港出生？

是 □1

否 □2 ⟶ 請註明地點：[ ]

9 char 50 NO

16. 孩子出生時，母親有多少歲？ [ ] 歲

10-98 99

不知道 □

17. 孩子出生時，父親有多少歲？ [ ] 歲

10-98 99

不知道 □

18. 孩子的父母曾否接受學校或職業訓練？

	母親	父親
沒有	□1/2	□1/2
小學	□1/2	□1/2
中學	□1/2	□1/2
大學 / 專上學院	□1/2	□1/2
其他技術訓練 （請註明）	□1/2（_____）	□1/2（_____）
	char 50 NO	char 50 NO

學童健康問題

19. 孩子的胸部過往有沒有**曾經**發出喘聲、氣緊或 He He 聲？

有 □1

沒有 □2 ⟶ **【如沒有，請跳往問題（25）】** 9

20. 孩子在**何時開始**有發出喘聲、氣緊或 He He 聲？

[ ] 歲 [ ] 個月

0-7 99 0-12 99

（若孩子在 1 歲 10 個月大時開始有以上病徵，就應在方格填上 1 歲 10 個月。）

21. **過去 12 個月內**，孩子的胸部有沒有發生喘聲、氣緊或 He He 聲？

有 □1

沒有 □2 ⟶【如沒有，請跳往問題（25）】 9

22. 過去 12 個月內，孩子曾有過多少次喘聲或氣緊？

沒有	□1	一至三次	□2
四至十二次	□3	十二次以上	□4

9

23. 過去 12 個月內，孩子平均有多少晚是**因為這些氣緊而從睡眠中醒過來**？

從沒有因氣緊而從睡眠中醒過來 □1

平均每星期少於一晚 □2

平均每星期一晚或多於一晚 □3 9

24. 過去 12 個月內，孩子有沒有因為氣喘到太嚴重而影響說話能力，每次吸氣只能講一至兩個字？

有 □1
沒有 □2 9

25. 孩子過往有沒有透過醫生或院方得知患上**哮喘**？

有 □1
沒有 □2 9

26. 孩子過往有沒有透過醫生或院方得知患上**氣管敏感**？

有 □1
沒有 □2 9

27. 孩子過往有沒有因氣喘而入住醫院？

有 □1
沒有 □2 9

28. 孩子過往除了氣喘之外，有沒有因為肺部不適入住醫院？

有 □1

沒有 ☐2 9

29. 孩子過往有沒有服用過氣喘（哮喘或氣管敏感）藥物？

有 ☐1
沒有 ☐2 9

30. 過去 12 個月內，孩子有沒有服用過氣喘（哮喘或氣管敏感）藥物？

有 ☐1
沒有 ☐2 9

31. 過去 12 個月內，孩子運動時或運動之後，胸部有沒有發生**喘聲或咳嗽**？

有 ☐1
沒有 ☐2 9

32. 過去 12 個月內，孩子在泳池內嗅到氯氣氣味時，胸部有沒有發生**喘聲或咳嗽**？

有 ☐1
沒有 ☐2 9

33. 過去 12 個月內，孩子在泳池游泳時，胸部有沒有發生**喘聲或咳嗽**？

有 ☐1
沒有 ☐2 9

34. 過去 12 個月內，除了患上傷風或肺部受感染的時候，孩子晚上有沒有乾咳？

有 ☐1
沒有 ☐2 9

問題 35-39 是指在沒有患上傷風或感冒時候的一般健康情況。

35. 孩子有沒有**曾經**患有打噴嚏、流鼻水或鼻塞問題？
（注意：傷風或感冒的時候不計算在內）

有 □1

沒有 □2 ⟶【如沒有，請跳往問題（40）】 9

36. 過去 12 個月內，孩子有沒有患有打噴嚏、流鼻水或鼻塞問題？
（注意：傷風或感冒的時候不計算在內）

有 □1

沒有 □2 ⟶【如沒有，請跳往問題（40）】 9

37. 過去 12 個月內，上列鼻部不適出現時，孩子有沒有同時出現流眼水和眼睛痕癢的問題？

有 □1
沒有 □2 9

38. 過去 12 個月內，上列鼻部不適怎樣影響孩子的日常生活？

毫無影響 □1
些微影響 □2
相當影響 □3
嚴重影響 □4 9

39. 過去 12 個月內，孩子在泳池游泳後，上列鼻或眼部不適等問題有否變得嚴重？

有 □1
沒有 □2 9

40. 孩子有沒有曾經患上鼻敏感？

有 □1
沒有 □2 9

---

41. 孩子有沒有一些痕疹持續半年或以上都未消散？

有 □1

沒有 □2 ⟶【如沒有，請跳往問題（48）】 9

42. 在孩子一歲前，這種痕疹有沒有發作？

有 □1
沒有 □2 9

43. 過去 12 個月內，這種痕疹有沒有發作？

有 □1

沒有 □2 ⟶【如沒有，請跳往問題（48）】 9

44. 過去 12 個月內，這種痕疹有沒有影響以下身體部位：手肘內側、膝頭後面、腳踝前面、臀部下端、頸、耳朵或眼睛四週？

有 □1
沒有 □2 9

45. 過去 12 個月內，這種痕疹有沒有完全消散？

有 □1
沒有 □2 9

46. 過去 12 個月內，孩子平均有多少晚是因為這種痕疹而不能入睡？

過去 12 個月內從沒有 □1
平均每星期少於一晚 □2
平均每星期一晚或多於一晚 □3 9

47. 過去 12 個月內，孩子在泳池游泳後，這種痕疹有否變得嚴重？

有 □1
沒有 □2 9

48. 孩子過往有沒有曾經患上濕疹？

有 □1
沒有 □2 9

49. 孩子**現在**有否戒吃某些食物？

有 ☐1 → 如果是“有”的話，請填寫這些食物：
_____
_____
char 50 NO

沒有 ☐2 9

50. 孩子過往有沒有**曾經**患上食物敏感？

有 ☐1
沒有 ☐2 9

51. 孩子過往有沒有透過醫生或院方，得知**患上食物敏感**？

有 ☐1
沒有 ☐2 → **【如沒有，請跳往問題（57）】** 9

52. 孩子**過往**有沒有因對食物產生不良反應而入住醫院？

有 ☐1 → 如果是“有”的話，共入院多少次？
一次 ☐1
兩次 ☐2
三次 ☐3
多於三次 ☐4 9

沒有 ☐2
9

53. **過去 12 個月內**，孩子曾有過多少次對食物的不良反應？

沒有 ☐1 一次 ☐2 兩次 ☐3
三次 ☐4 四次或以上 ☐5 9

54. **過去 12 個月內**，孩子有沒有因對食物產生不良反應而入住醫院？

有 ☐1 → 如果是“有”的話，過往共入院多少次？
一次 ☐1
兩次 ☐2
三次 ☐3
多於三次 ☐4 9

沒有 ☐2
9

55. **<u>過去 12 個月內</u>**，上列食物不良反應怎樣影響孩子的日常生活？

沒有影響	☐1	些微影響	☐2
相當影響	☐3	嚴重影響	☐4

9

56. 請註明孩子**<u>過往</u>**對食物產生的不良反應（可以選擇多於一個答案）：

食物名稱：__________ char 50 NO

皮膚出疹	☐1	皮膚腫脹	☐2
嘔吐，作嘔	☐3	肚痛	☐4
肚瀉	☐5	呼吸困難	☐6
過敏性休克	☐7	其他反應	☐8

9

食物名稱：__________ char 50 NO

皮膚出疹	☐1	皮膚腫脹	☐2
嘔吐，作嘔	☐3	肚痛	☐4
肚瀉	☐5	呼吸困難	☐6
過敏性休克	☐7	其他反應	☐8

9

食物名稱：__________ char 50 NO

皮膚出疹	☐1	皮膚腫脹	☐2
嘔吐，作嘔	☐3	肚痛	☐4
肚瀉	☐5	呼吸困難	☐6
過敏性休克	☐7	其他反應	☐8

9

（如對多於三種食物產生反應，請另加紙張填寫）

飲食和環境因素

57. 孩子是否由母乳餵養？

否 ☐2
是 ☐1 →
9

<u>若答案是“是”的話</u>，

有多久？

少於 6 個月	☐1
6 至少於 12 個月	☐2
12 個月或以上	☐3

9

孩子有多久是只用母乳，而沒有添加其他食物或飲料餵養？

少於 2 個月	☐1
2 至少於 4 個月	☐2
4 至少於 6 個月	☐3
6 個月或以上	☐4

9

58. 孩子有多少個**哥哥或姐姐**？

沒有 2 ☐ 9

有 1，共有 ☐☐ 個

1-98 99

59. 孩子有多少個**弟弟或妹妹**？

沒有 2 ☐ 9

有 1，共有 ☐☐ 個

1-98 99

60. 孩子是否入讀過托兒所或育嬰院？

否 ☐2

是 ☐1 → 9

若答案是“是”的話，

首次入讀是在何年齡？ ☐☐ 歲 ☐☐ 個月

0-7 99 0-12 99

（若孩子在**２歲８個月大**時入讀過托兒所或育嬰院，
就應在方格填上**２歲８個月**。）

入讀多久？

少於 6 個月 ☐1

6 至 12 個月 ☐2

多於 12 個月 ☐3 9

61. 孩子有否學習游泳？

沒有 □2
有 □1 ⟶

9

若答案是“有”的話，

孩子**最初**習泳時有多大？

1 歲前	□1	
1 歲至 2 歲	□2	
3 歲或以後	□3	9

孩子**多數**習泳的地點為：

室內泳池	□1	
室外泳池	□2	
海灘	□3	
其他	□4	9

過去 12 個月內，孩子**平均**習泳的次數為：

每週 3 次或以上	□1	
每週 1 至 2 次	□2	
每月 1 至 3 次	□3	
少於每月 1 次	□4	9

62. 孩子的母親曾否患有以下的疾病？（**可以選擇一個或以上的答案**）

哮喘	□1/2
鼻敏感	□1/2
濕疹	□1/2
食物敏感	□1/2
沒有	□1/2
不知道	□1/2

63. 孩子的父親曾否患有以下的疾病？（**可以選擇一個或以上的答案**）

哮喘	□1/2
鼻敏感	□1/2
濕疹	□1/2
食物敏感	□1/2
沒有	□1/2
不知道	□1/2

64. 如果孩子有**哥哥或弟弟**，請問孩子的**哥哥或弟弟**曾否患有以下的疾病？
（**可以選擇一個或以上的答案**）

哮喘 ☐1/2
鼻敏感 ☐1/2
濕疹 ☐1/2
食物敏感 ☐1/2
沒有 ☐1/2
不知道 ☐1/2

65. 如果孩子有**姊姊或妹妹**，請問孩子的**姊姊或妹妹**曾否患有以下的疾病？
（**可以選擇一個或以上的答案**）

哮喘 ☐1/2
鼻敏感 ☐1/2
濕疹 ☐1/2
食物敏感 ☐1/2
沒有 ☐1/2
不知道 ☐1/2

在以下問題中，“家”是指孩子大部份時間居住的地方。

66. 孩子和多少個人共用睡房？（**孩子本人<u>不計算</u>在內**）

現在 [ ] 人 0-98 99
在孩子一歲前 [ ] 人 0-98 99

67. 你有否在家中飼養下列寵物？（可以選擇一個或以上的答案）

	現在	在孩子一歲前
狗	☐1/2	☐1/2
貓	☐1/2	☐1/2
其他有毛寵物	☐1/2	☐1/2
雀鳥	☐1/2	☐1/2
其他（請註明）	☐1/2（_____） char 50 NO	☐1/2（_____） char 50 NO
沒有	☐1/2	☐1/2

68. 孩子是否經常接觸到下列戶外動物？（可以選擇一個或以上的答案）

現在 在孩子一歲前

狗	□1/2	□1/2
貓	□1/2	□1/2
農場動物	□1/2	□1/2
其他有毛寵物	□1/2	□1/2
沒有	□1/2	□1/2

69. 孩子過往有沒有在農場居住？

沒有 □2 ⟶ **【如沒有，請跳往問題（71）】**

有 □1 ⟶

9

70. 你在農場從事那一種活動？

當孩子在 1 歲之前的時候：	有	沒有	
農業耕種	□1	□2	9
飼養禽畜	□1	□2	9

當孩子在 1 至 2 歲的時候：	有	沒有	
農業耕種	□1	□2	9
飼養禽畜	□1	□2	9

當孩子在 2 歲之後的時候：	有	沒有	
農業耕種	□1	□2	9
飼養禽畜	□1	□2	9

若答案是“有”的話，在農場居住時，孩子的年齡是？

	有	沒有	
1 歲之前	□1	□2	9
1 至 2 歲	□1	□2	9
2 歲之後	□1	□2	9
現在	□1	□2	9

現在：	有	沒有	
農業耕種	☐1	☐2	9
飼養禽畜	☐1	☐2	9

71. 孩子的母親是否吸煙？

	有	沒有	
現在	☐1	☐2	9
在孩子一歲前	☐1	☐2	9
懷孕著孩子的時候	☐1	☐2	9

72. 現在和孩子居住的人有沒有吸煙？

沒有 ☐2

有 ☐1 ⟶ 9

73. 你是用何種燃料煮食？

（可以選擇一個或以上的答案，請在適當的方格加上 ☑ 。）

	現在	在孩子一歲前
電力	☐1/2	☐1/2
煤氣 / 石油氣	☐1/2	☐1/2
煤 / 木柴	☐1/2	☐1/2
火水（煤油）	☐1/2	☐1/2

74. 你用何種燃料作為取暖用途？

（可以選擇一個或以上的答案，請在適當的方格加上 √ 。）

<u>如果是“有”的話</u>，每天在家裏吸多少枝煙？

少於 10 枝	☐1
10 至 20 枝	☐2
多於 20 枝	☐3

9

	現在	在孩子一歲前
煤氣 / 石油氣	☐1/2	☐1/2
油	☐1/2	☐1/2
電力	☐1/2	☐1/2
煤	☐1/2	☐1/2
木柴	☐1/2	☐1/2
不知道	☐1/2	☐1/2
沒有用燃料取暖	☐1/2	☐1/2

75. 孩子的家裏有沒有冷氣機？

沒有 ☐2
有 ☐1 → 9

<u>如果是“有”的話</u>，是安裝在：（你可以選擇多個答案）
客廳 ☐1/2
孩子的睡房 ☐1/2

76. 孩子家裏的天花板或牆壁是否有**潮濕或發霉的痕跡**？

	有	沒有	
現在	☐1	☐2	9
在孩子一歲前	☐1	☐2	9

77. 孩子的睡房是用那種地面？

	現在		在孩子一歲前	
地氈	☐1/2		☐1/2	
木地板 / 地磚	☐1/2		☐1/2	
其他（請註明）	☐1/2	（_____）	☐1/2	（_____）
		char 50 NO		char 50 NO

78. 孩子是用那種枕頭？

	現在		在孩子一歲前	
棉花	☐1/2		☐1/2	
乳膠	☐1/2		☐1/2	
人工合成纖維	☐1/2		☐1/2	
羽毛	☐1/2		☐1/2	
沒有用枕頭	☐1/2		☐1/2	
其他（請註明）	☐1/2	（_____）	☐1/2	（_____）
		char 50 NO		char 50 NO

79. 孩子是用那種被子？

	現在		在孩子一歲前	
棉花	☐1/2		☐1/2	
人工合成纖維	☐1/2		☐1/2	
羽毛	☐1/2		☐1/2	
毛氈	☐1/2		☐1/2	
其他（請註明）	☐1/2	（_____）	☐1/2	（_____）
		char 50 NO		char 50 NO

80. 你是否因為孩子的**哮喘或過敏問題**而做出以下轉變？

放棄養寵物　　否 □2
是 □1 → <u>若答案是“是”的話</u>，
9　在孩子 [　　] 歲。
0-7　99

停止或減少吸煙　　否 □2
是 □1 → <u>若答案是“是”的話</u>，
9　在孩子 [　　] 歲。
0-7　99

換另一種床單，被舖或枕頭　　否 □2
是 □1 → <u>若答案是“是”的話</u>，
9　在孩子 [　　] 歲。
0-7　99

停止或減少在泳池游泳　　否 □2
是 □1 → <u>若答案是“是”的話</u>，
9　在孩子 [　　] 歲。
0-7　99

（若你在孩子**2歲大**時因他／她的過敏問題而做出以上轉變，就應在方格填上**2歲**。）

81. <u>過去 12 個月內</u>，孩子有沒有服用止痛、退燒藥？（例如：「必理痛」）

沒有 □2
有 □1 →
9

<u>如果是“有”的話</u>，次數平均有多少？
平均一年至少一次 □1
平均一個月至少一次 □2　9

---

82. 孩子的體重：____公斤/磅* 和 身高：_____米/厘米/呎 *（請選擇適當的量度單位）
1.0-99.8　50-200　99.9

83. 出世時周歲：____月/周

84. 出世時體重：____公斤/磅

******* 問卷完，多謝閣下參與此項調查 *******

兒童及青少年健康問卷

Subject No:_____－_____

當日號碼

Q1. 學校名稱：_____

Q2. 學生姓名：_____

Q3. 班級： _____(_____)

Q4. 性別： □1.男 □2.女

Q5. 出生日期： _____年_____月_____日

Q6. 出生時體重： _____磅 / _____公斤

Q7. 出生時之懷孕周數：□1.足月（> = 37 周） □2.早產（懷孕周數）_____周

Q8.a 孩子在出生後是否由母乳餵養？

□ 1.是 ⟶
□ 2.沒有

b.若答案為“是”的話，
有多久？ □ 1. 少於 4 個月
□ 2. 4 至 6 個月
□ 3. 多於 6 個月

孩子有否患有以下疾病：

Q9.	高血壓	□ 1.有	□ 2.沒有
Q10.	慢性腎病	□ 1.有	□ 2.沒有
Q11.	睡眠窒息症	□ 1.有	□ 2.沒有
Q12.	類風濕關節炎	□ 1.有	□ 2.沒有

孩子睡眠常態：請填 24 小時制 (例: 晚上 9 時正—填寫 21 時 00 分)

Q13. 星期一至五,他/她每晚通常甚麼時候上床睡覺? _____時:____分
Q14. 星期一至五,他/她每天通常甚麼時候起床? _____時:____分
Q15. 星期六、日或假期不用上學的時候, 他/她每晚通常甚麼時候上床睡覺? _____時:____分
Q16. 星期六、日或假期不用上學的時候, 他/她每天通常甚麼時候起床? _____時:____分

Q17. 在過往12個月內, 他/她有沒有打鼻鼾呢?
0□ 從不 1□ 每月少於一晚
2□ 每週有一至兩晚 3□ 每週有三晚或以上

Q18. 續上題(若上題答案是1-3), 幾多歲開始有鼻鼾聲呢? □ **歲 /** □ 沒有
(若上題 Q17 答案是 0, 請選沒有)

Q19. a 除體育課外孩子每週有否接受其它定期的體育訓練？

□ 1. 是 ⟶
□ 2. 沒有

b.若答案為“是”的話，
有多久？ □ 1. 一次
□ 2. 兩次
□ 3. 三次或以上

(後頁再續)

過往 12 個月的飲食習慣 (請在適當的答案上加 √)

	0.從不	1.很少 (每月小於 1 次)	2.間中 (每月數次)	3.經常 (每周數次)	4.每日
Q20. 油炸食物 (如炸雞脾, 油炸鬼…)					
Q21. 午餐肉					
Q22. 腸仔					
Q23. 街邊魚蛋					
Q24. 雞蛋仔/格仔餅					
Q25. 鹹魚/鹹蛋					
Q26. 即食麵					
Q27. 麥當勞快餐					
Q28. 肯德基快餐					
Q29. 其它快餐店食品					
Q30. 酒樓食品					
Q31. 意大利粉					
Q32. 薄餅					
Q33. 餅乾					
Q34. 薯片/蝦條					
Q35. 芝士蛋糕					
Q36. 朱古力					
Q37. 糖果					
Q38. 雪糕					
Q39. 汽水					
Q40. 水果					
Q41. 蔬菜					
Q42. 麥皮					

Q43. 是否喜歡吃較鹹或濃味食物： □ 1. 是 □ 2. 間中 □ 3. 否

Q44. 父親教育程度： □ 1. 小學或以下 □ 2. 初中程度 □ 3. 高中程度 □ 4.大專或以上

Q45. 母親教育程度： □ 1. 小學或以下 □ 2. 初中程度 □ 3. 高中程度 □ 4.大專或以上

家庭病歷資料：請在 □ 內加√(可以選擇一個或以上的答案)

Q46. 父親

□ 1.高血壓 □ 2.中風 □ 3.冠心病 □ 4.糖尿病 □ 5.肥胖症 □ 6. 沒有

Q47. 母親

□ 1.高血壓 □ 2.中風 □ 3.冠心病 □ 4.糖尿病 □ 5.肥胖症 □ 6. 沒有

學校名稱：_____

Subject No:_____

兒童及青少年健康問卷 Ⅱ

香港中文大學醫學院兒科學系現向全港 8-17 歲兒童及青少年搜集有關過敏性鼻炎的相關資料，貴校已同意參與此項重要和有意義的調查，希望閣下能提供以下資料，謝謝！

填寫問卷日期： ____日____月____年

學生姓名：_____

學生電話(家/手提)： _____ **Email**： _____

性別： ☐ **1.** 男 ☐ **2.** 女

種族： ☐ **1.** 華人 ☐ **2** 非華人

出生日期： ____日____月____年

身高： _____**cm** 體重： _____**kg**

孩子在出生後是否由母乳餵養？

否 ☐
是 ☐ → 若答案為“是”的話，
有多久？ 少於 4 個月 ☐ 4 至 6 個月 ☐
多於 6 個月 ☐

孩子有多少個哥哥或姐姐？

沒有 ☐
有，共有 ☐ 個

孩子有多少個弟弟或妹妹？

沒有 ☐
有，共有 ☐ 個

孩子的母親曾否患有以下的疾病？（可以選擇一個或以上的答案）

哮喘 ☐ 鼻敏感 ☐
濕疹 ☐ 食物敏感 ☐ （甚麼食物：_____）
氣管敏感 ☐ 藥物 ☐（請註明：_____）

孩子的父親曾否患有以下的疾病？（可以選擇一個或以上的答案）

哮喘 ☐ 鼻敏感 ☐
濕疹 ☐ 食物敏感 ☐ （甚麼食物：_____）
氣管敏感 ☐ 藥物 ☐（請註明：_____）

(後頁再續)

如果孩子有哥哥或弟弟，請問孩子的哥哥或弟弟曾否患有以下的疾病？
（可以選擇一個或以上的答案）

哮喘 ☐　　鼻敏感 ☐
濕疹 ☐　　食物敏感 ☐ （甚麼食物：_____）
氣管敏感 ☐　　藥物 ☐ （請註明：_____）

如果孩子有姊姊或妹妹，請問孩子的姊姊或妹妹曾否患有以下的疾病？
（可以選擇一個或以上的答案）

哮喘 ☐　　鼻敏感 ☐
濕疹 ☐　　食物敏感 ☐（甚麼食物：_____）
氣管敏感 ☐　　藥物 ☐（請註明：_____）

你現在有否在家中飼養下列寵物？（可以選擇一個或以上的答案）

狗 ☐(品種:_____)　　貓 ☐(品種:_____)
其他 ☐(請註明:_____）

現在和孩子居住的人有沒有吸煙？

沒有 ☐
有 ☐ →

如果是“有”的話，是誰人？
父親 ☐
母親 ☐
其他人（請註明） ☐（_____）

以上各人每天在家裏合共吸多少枝煙？
少於 10 枝 ☐　　10 至 20 枝 ☐
多於 20 枝 ☐

現在，孩子家裏的天花板或牆壁是否有潮濕或發霉的痕跡？

有 ☐　　沒有 ☐

過去 **4** 星期內，孩子有沒有服用抗生素？

沒有 ☐
有 ☐(請註明名稱:_____)

過去 **4** 星期內，孩子有沒有看醫生？

沒有 ☐
有 ☐(請註明原因:_____) →
☐私家醫生就診
☐政府醫院就診

過去 **12** 個月內，孩子有沒有住院？

有 ☐(請註明原因:_____)　　沒有 ☐

（以下問題，請在適當的答案空格上加上「✓」號）

有沒有醫生為你的孩子診斷患上哮喘？ ☐ 有 ☐ 沒有

有沒有醫生為你的孩子診斷患上氣管敏感？ ☐ 有 ☐ 沒有

有沒有醫生為你的孩子診斷患上濕疹？ ☐ 有 ☐ 沒有

你的孩子有沒有曾經或現在患上食物敏感？ ☐ 有 ☐ 沒有

（請註明是甚麼食物：_____）

你的孩子在<u>沒有</u>患上傷風或感冒的時候，有沒有下列情況？

<u>過去 12 個月內</u>，你的孩子有沒有打噴嚏，流鼻水或鼻塞問題？
(注意：傷風或感冒的時候<u>不計算在內</u>)

☐ 有　　☐ 沒有

《 若您的答案是〔沒有〕，請不用作答以下問題 》

<u>過去 12 個月內</u>，你的孩子有沒有
流眼水和眼睛痕癢的問題？ ☐ 有 ☐ 沒有

<u>12 個月內</u>，上列鼻部不適
在那些月份出現？
(請在適當的月份加上「√」號）

☐ 一月 ☐ 二月 ☐ 三月 ☐ 四月
☐ 五月 ☐ 六月 ☐ 七月 ☐ 八月
☐ 九月 ☐ 十月 ☐ 十一月 ☐ 十二月

(後頁再續)

孩子家裏有没有下列可以誘發敏感病發的因素?

a) 毛公仔	□没有	□有
b) 地毯	□没有	□有
c) 布窗簾/百葉簾	□没有	□有
d) 高濕度	□没有	□有
e) 塵埃 / 污濁的空氣	□没有	□有
f) 蟑螂	□没有	□有
g) 開花植物	□没有	□有
h) 某些食品，請註明: _____	□没有	□有
i) 某些藥物，請註明: _____	□没有	□有

j) 會否使用熱水 (攝氏 65 度以上的水) 清洗小朋友使用的被單,床單或枕頭袋嗎？ □ 不會 □ 會

過去 12 個月內，上列鼻部不適怎樣影響你孩子的日常生活？(如不能接觸寵物，或打掃時發病)	□ 毫無影響	□ 些微影響	□ 相當影響	□ 嚴重影響
過去 12 個月內，上列鼻部不適有沒有影響你孩子的睡眠？(如不能入睡、或夜半驚醒、難再入眠)	□ 毫無影響	□ 些微影響	□ 相當影響	□ 嚴重影響
過去 12 個月內，上列鼻部不適有沒對你的孩子做成困擾？(如因經常擦鼻，打噴嚏而感到尷尬)	□ 毫無影響	□ 些微影響	□ 相當影響	□ 嚴重影響

有沒有醫生為你的孩子診斷患上鼻敏感？	□ 有	□ 沒有
你孩子的鼻敏感病徵是否每星期出現 4 天或更多，而且持續 4 星期或以上？	□ 是	□ 否

探討重金屬對香港兒童的生長和發展的影響

（兒童問卷）

Name 姓名: _____

(_____)

Gum Label

性別: _____

Age 年齡: _____

Height 身高: _____cm

Weight 體重: _____kg

慢性疾病 Chronic medical diseases: *

☐ (1) Yes 有

☐ (2) No 無

**如答有，請詳列 If yes, details:*

☐ Heart 心臟病 (1)

☐ Lung 肺病 (2)

☐ Kidney 腎病 (3)

☐ Liver 肝病 (4)

☐ Neurological disorders (e.g., epilepsy 癲閒) (5)

☐ Asthma 哮喘 (6)

☐ Allergic rhinitis 過敏鼻炎 (7)

☐ Eczema 濕疹 (8)

☐ Malignancy 癌症 (9)

☐ Psychiatric illness 精神病 (10)

☐ Psychological problems 心理問題(e.g., 小兒多動症 ADHD) (11)

☐ Others _____ (12)

Head injuries 頭顱損傷

☐ (1) Yes 有

☐ (2) No 無

**如答有，請詳列 If yes, details:*

- 住院 Hospitalised?

☐ (1) Yes 有

☐ (2) No 無

- 頭部掃描 CT brain?

☐ (1) Yes 有

☐ (2) No 無

- (3)手術 Surgery?

☐ (1) Yes 有

☐ (2) No 無

- 日期 Date _____

Recurrent minor illnesses 有否經常出現以下疾病 (一年有數次):

URTI 上呼吸道感染(感冒)

☐ (1) Yes 有

☐ (2) No 無

GE 腸胃炎（腹瀉）

☐ (1) Yes 有

☐ (2) No 無

Other illnesses 其它 _____

☐ (1) Yes 有

☐ (2) No 無

Major acute illnesses requiring hospitalisation 有否因急病住院:

☐ (1) Yes 有 Episode 1 Episode 2 Episode 3

- 診斷 Diagnosis? _____ _____ _____
- 住院時間 Length of stay? _____ _____ _____
- 入院日期 Date _____ _____ _____

☐ (2) No 無

Major surgery 曾進行外科手術

☐ (1) Yes 有 Episode 1 Episode 2 Episode 3

- 診斷 Diagnosis? _____ _____ _____
- 住院時間 Length of stay? _____ _____ _____
- 入院日期 Date _____ _____ _____

☐ (2) No 無

Regular medications 有否需要定期服藥:

☐ (1) Yes 有 _____

☐ (2) No 無

Family history of major illnesses, asthma/atopy 家庭成員有否患有過敏疾病 (哮喘/過敏性鼻炎/濕疹)

☐ (1) Yes 有 Relative 1 Relative 2 Relative 3

- **哮喘** Asthma? _____ _____ _____
- **過敏性鼻炎** Allergic rhinitis? _____ _____ _____
- **濕疹** Eczema? _____ _____ _____

☐ (2) No 無

Vaccination history 有否免疫注射

☐ (1) Up-to-date (according to HK schedule) 根據香港規定接受注射

☐ (2) Not up to date 無據香港規定接受注射

已接受的疫苗 Vaccines given _____

☐ (3) Other vaccines 其它

已接受的疫苗 Vaccines given (e.g., 水豆 chicken pox, 輪狀病毒 rotavirus,)

_____

Birth history

第幾胎 Parity_____

Mode of delivery 生產方式

- (1)Vaginal delivery 順產
- (2)Caesarean section 剖宮產
- (3)Vacuum extraction 吸產
- (4)Other 其它

出生體重 Birth weight _____ kg

孕週數 Gestation _____ weeks

出生後第一個月有否住院 Hospitalisations within the first month of life?

- (1)Yes 有 Episode 1 Episode 2 Episode 3

- 診斷 Diagnosis? _____ _____ _____
- 住院時間 Length of stay? _____ _____ _____
- 入院日期 Date _____ _____ _____

- (2)No 無

睡眠 Sleep

☐ (1) 打鼾 Does your child snore when he/she is asleep?

1. Yes 有 2. No 无

☐ (2) 日間嗜睡 Does your child have any daytime sleepiness?

1. Yes 有 2. No 无

☐ (3) 夜間睡眠時間 Hours of sleep at night:

- 週日 Weekdays _____ 小時 hours/night
- 週末 Weekends _____ 小時 hours/night

Language 語言:

☐ (1) Cantonese 粵語

☐ (2) Putonghua 普通話

☐ (3) English 英語

☐ (4) Others 其它 _____

就讀 Schooling:

☐ (1) 幼稚園 Kindergarten _____

☐ (2) 小學 Primary school _____

☐ (3) Others 其它 _____

嬰兒期喂哺情況 Baby feeding

奶粉 Formula milk: 1.yes 有 2.no 無

Duration: _____ (age of the baby)

母乳 Breast milk: 1.yes 有 2.no 無

Duration: _____ (age of the baby)

戒奶年齡 Weaning time: _____ (age of the baby)

何時給予副食品 Food supplement: _____ (age of the baby)

居住環境

Any carpets 家中有否使用地毯

☐ (1) Yes 有

☐ (2) No 無

Any furry pets/toys 有否玩毛公仔

☐ (1) Yes 有

☐ (2) No 無

Burning of joss-sticks at home 家中有否燒香

☐ (1) Yes 有

☐ (2) No 無

每週燒香的次數: _____

Household smokers 家中有否吸煙者

☐ (1) Yes 有

☐ (2) No 無

Main carer 兒童的照顧者

1. 父親 Father

2. 母親 Mother

3. 祖父母 Grandparent

4. Domestic helper 傭人

5. Other 其它

Educational background of the main carer 兒童的照顧者的教育程度

☐ (1) University / College 大學

☐ (2) High School 高中

☐ (3) F1 to F3 中一至中三

☐ (4) Primary School and below 小學或以下

☐ (5) None 沒有

Language of the main carer 兒童的照顧者的語言

☐ (1) Cantonese 廣州話

☐ (2) Putonghua 普通話

☐ (3) English 英語

☐ (4) Others 其它 _____

Occupation of the main carer 兒童的照顧者的職業

☐ (1) Housewife 家庭主婦

☐ (2) Professional 專業人士

☐ (3) Manual 手作工

☐ (4) Non-manual 非手作工

☐ (5) Domestic helper 家庭傭工

Does the main carer smoke 兒童的照顧者有否抽煙習慣

☐ (1) Yes 有

☐ (2) No 無

**If yes 如答有:*

Quantity 數量: 每月_____根 cigarettes per month

探討重金屬對香港兒童的生長和發展的影響

（父母親問卷）

Serial no 編號: _____

Address 住址: _____

_____

Gum Label

Mother 母親

Name 姓名: _____ (_____)

Age 年齡: _____

Occupation 職業:

☐ (1) Housewife 家庭主婦

☐ (2) Professional 專業人士

☐ (3) Manual 手作工

☐ (4) Non-manual 非手作工

☐ (5) Fisherman 漁民

☐ (6) Fishery industry 漁業

Occupational exposure 工作時會否暴露於:

☐ (1) Yes 是

☐ (2) No 否

Details:

☐ Chlorine and caustic soda production 氯化物與哥士的 (1)

☐ Mining and metallurgy 採礦與金工物料 (2)

☐ Electroplating電鍍物料 (3)

☐ Chemical and textile manufacturing 化學與製衣物料(4)

☐ Wood 木工物料 (5)

☐ Plastics and paper processing 塑膠與紙張製造物料 (6)

☐ Leather tanning 皮革製造物料 (7)

☐ Pharmaceutical manufacturing 藥劑製造物料 (8)

☐ Ceramic ware manufacturing 陶瓷製造物料 (9)

Education 教育程度:

☐ (1) University / College 大學

☐ (2) High School 高中

☐ (3) F1 to F3 中一至中三

☐ (4) Primary School and below 小學或以下

☐ (5) None 沒有

NS-SEC Occupation:

☐ (1) Modern professional occupations 現代專業人士

☐ (2) Clerical and intermediate occupations 中級文職人員

☐ (3) Senior managers or administrators 管理階層

☐ (4) Technical and craft occupations 技術人員

☐ (5) Semi-routine manual and service occupations 半手作服務

☐ (6) Routine manual and service occupations 工人

☐ (7) Middle or junior managers 中層或基層管理人員

☐ (8) Traditional professional occupations 傳統專業人士

NS-SEC employment status:

☐ (1) Employers – large organisations

☐ (2) Employers – small organisations

☐ (3) Self-employed, no employees

☐ (4) Managers – large organisations

☐ (5) Managers – small organisations

☐ (6) Supervisors

☐ (7) Other employees

NS-SEC Class:

☐ (1) Managerial and professional occupations

☐ (2) Intermediate occupations

☐ (3) Small employers and own account workers

☐ (4) Lower supervisory and technical occupations

☐ (5) Semi-routine and routine occupations

Language 語言:

☐ (1) Cantonese 粵語

☐ (2) Putonghua 普通話

☐ (3) English 英語

☐ (4) Others 其它 _____

住宅 Type of residence:

☐ (1) Private 私人住宅

☐ (2) Public Housing 公共屋村

☐ (3) Others 其他_____

Age of house/apartment 樓齡 _____ years

Size of living quarters 住宅面積 _____ 平方呎

Number of rooms 戶間數目 _____

Number of people living in house/apartment 居住人數_____

Alcohol consumption 酒類飲用:*

☐ (1) Yes 有

☐ (2) No 無

☐ (3) Social drinker

**如答有，請指出酒類飲料之種類 If yes, type of alcohol consumption:*

☐ beer 啤酒 (1)

☐ brandy 白蘭地 (2)

☐ whisky 威士己 (3)

☐ white wine 白酒 (4)

☐ red wine 紅酒 (5)

☐ Chinese wine 中國酒 (6)

☐ other 其他 (7)

Quantity 份量: 每月_____ 杯 glasses per month 已有 for _____ 年 years

Smoking 抽煙情況: *

☐ (1) Yes 有

☐ (2) No 無

**If yes 如答有:*

Quantity 數量: 每月_____根 cigarettes per month for 已有 _____ 年 years

慢性疾病 Chronic medical diseases: *

☐ (1) Yes 有

☐ (2) No 無

**如答有，請詳列 If yes, details:*

☐ Heart 心臟病 (1)

☐ Lung 肺病 (2)

☐ Kidney 腎病 (3)

☐ Liver 肝病 (4)

☐ Neurological disorders (e.g., epilepsy 癲閒) (5)

☐ Asthma 哮喘 (6)

☐ Allergic rhinitis 過敏鼻炎 (7)

☐ Eczema 濕疹 (8)

☐ Malignancy 癌症 (9)

☐ Psychiatric illness (10)

☐ Psychological problems (11)

☐ Others _____ (12)

Father 父親

Place of birth 出生地: _____

Age 年齡: _____

Education 教育程度:

☐ (1) University / College 大學

☐ (2) High School 高中

☐ (3) F1 to F3 中一至中三

☐ (4) Primary School and below 小學或以下

☐ (5) None 沒有

Occupation 職業:

☐ (1) Unemployed 無業

☐ (2) Professional 專業人士

☐ (3) Manual 手作工

☐ (4) Non-manual 非手作工

☐ (5) Fisherman 漁民

☐ (6) Fishery industry 漁業

NS-SEC Occupation:

☐ (1) Modern professional occupations

☐ (2) Clerical and intermediate occupations

☐ (3) Senior managers or administrators

☐ (4) Technical and craft occupations

☐ (5) Semi-routine manual and service occupations

☐ (6) Routine manual and service occupations

☐ (7) Middle or junior managers

☐ (8) Traditional professional occupations

NS-SEC employment status:

☐ (1) Employers – large organisations

☐ (2) Employers – small organisations

☐ (3) Self-employed, no employees

☐ (4) Managers – large organisations

☐ (5) Managers – small organisations

☐ (6) Supervisors

☐ (7) Other employees

NS-SEC Class:

☐ (1) Managerial and professional occupations

☐ (2) Intermediate occupations

☐ (3) Small employers and own account workers

☐ (4) Lower supervisory and technical occupations

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Language 語言:

☐ (1) Cantonese 粵語

☐ (2) Putonghua 普通話

☐ (3) English 英語

☐ (4) Others 其它 _____

Smoking 抽煙情況: *

☐ (1) Yes 有

☐ (2) No 無

**If yes 如答有:*

Quantity 數量: 每月_____根 cigarettes per month for 已有 _____ 年 years

Alcohol consumption 酒類飲用:*

☐ (1) Yes 有

☐ (2) No 無

☐ (3) Social drinker

**如答有，請指出酒類飲料之種類 If yes, type of alcohol consumption:*

☐ beer 啤酒 (1)

☐ brandy 白蘭地 (2)

☐ whisky 威士已 (3)

☐ white wine 白酒 (4)

☐ red wine 紅酒 (5)

☐ Chinese wine 中國酒 (6)

☐ other 其他 (7)

Quantity 份量: 每月_____ 杯 glasses per month 已有 for _____ 年 years

慢性疾病 Chronic medical diseases: *

☐ (1) Yes 有

☐ (2) No 無

**如答有，請詳列 If yes, details:*

☐ Heart 心臟病 (1)

☐ Lung 肺病 (2)

☐ Kidney 腎病 (3)

☐ Liver 肝病 (4)

☐ Neurological disorders (e.g., epilepsy 癲閒) (5)

☐ Asthma 哮喘 (6)

☐ Allergic rhinitis 過敏鼻炎 (7)

☐ Eczema 濕疹 (8)

☐ Malignancy 癌症 (9)

☐ Psychiatric illness (10)

☐ Psychological problems (11)

☐ Others _____ (12)

Monthly family income 家庭每月收入 HK$:

☐ (1) < $ 10000

☐ (2) $10000- $20000

☐ (3) $20000-$30000

☐ (4) $30000-$40000

☐ (5) >$40000

香港兒童睡眠調查

【家長評核問卷】

姓名: _____ 編號: _____

(接受調查之兒童) (本院填寫)

電話: _____ 填寫日期: ___/___/___ (日/月/年)

主要資料來源提供者:

1□ 父親 2□ 母親 3□ 近親 (_____) 4□ 其他: _____

研究目的旨在瞭解接受問卷調查之兒童在最近一年內的日常睡眠習慣，如閣下不清楚該名兒童的睡眠情況，請諮詢其他家庭成員，並選擇最合適的答案。

**本問卷總共有 5 頁 54 條問題，請在適當的方格裡加上 "✓" ，並盡量回答所有問題，不要填漏，多謝合作！

*** 所有資料只供研究用途,絕對保密 ***

(A) 兒童的個人資料

1) 性別： 1□ 男 2□ 女

2) a. 出生日期(日/月/年)： _____ /_____/_____

b. 出生地點： 1□ 香港 2□ 中國 (在港居住年期: __年__月) 3□ 其他 (在港居住年期: __年__月)

c. 名字(英文)： _____

3) a. 身高：_____ (厘米) b. *體重：_____ (千克 / 磅) {*請刪去不適用者}

4) 居住情況：(可 **"✓"** 多項選擇)

a. 1□ 與父母同住 2□ 與父親同住 3□ 與母親同住 4□ 與親戚同住 5□ 其他：_____

b. 包括這兒童在內, 現時有多少人同住：_____

c. 他/她有多少個兄弟姊妹：_____

5) 教育程度：

a. 年級： _____ (請填上現時就讀的班級)

b. 時間： 1□ 上午班 2□ 下午班 3□ 全日

(B) 兒童在『最近一年』內的睡眠狀況

6) 這兒童通常都是**自己睡一間房**嗎?

1□ 是 0□ 不是 (和_____同睡一間房)

7) 他/她通常都是**自己睡一張床**嗎?

1□ 是 0□ 不是 (和_____同睡一間床)

8) a.i. **星期一至五**, 他/她每晚通常甚麼時候**上床**睡覺? _____時:____分

ii. **星期一至五**, 他/她每天通常甚麼時候**起床**? _____時:____分

b.i. **星期六、日**不用上學的時候, 他/她每晚通常甚麼時候**上床**睡覺? _____時:____分

ii. **星期六、日**不用上學的時候, 他/她每天通常甚麼時候**起床**? _____時:____分

c.i. **在長假期或暑假裡**, 他/她每晚通常甚麼時候**上床**睡覺? _____時:____分

ii. **在長假期或暑假裡**, 他/她每天通常甚麼時候**起床**? _____時:____分

9) 他/她通常**需要多少時間才能入睡**?

1□ 少於10分鐘 2□ 11-30分鐘 3□ 31-60分鐘 4□ 超過60分鐘

10) 他/她最近一年內**平均每晚睡多少時間**? _____小時_____分鐘

11) a. 你認為他/她**得到足夠的睡眠**嗎? 1□ 足夠 0□ 不足夠

b. 你認為他/她需要**睡多久才足夠**? _____小時_____分鐘

以下是一系列有關這兒童在**過往一年內**的睡眠情況，請選擇下列每一項描述所發生的次數：

	從不	每月少於一次	每月一至兩次	每週一至兩次	每週三次或以上	不清楚
12) 晚上**難以入睡**	0□	1□	2□	3□	4□	5□
13) 將入睡時，感到**憂慮或恐懼**	0□	1□	2□	3□	4□	5□
14) 將入睡時，**頭部重覆地搖動或碰撞**	0□	1□	2□	3□	4□	5□
15) 睡覺時，**手或腳經常不隨意地抽搐或跳動**	0□	1□	2□	3□	4□	5□
16) 睡覺時**經常流汗**	0□	1□	2□	3□	4□	5□
17) 睡至半夜會“**扎**”醒	0□	1□	2□	3□	4□	5□
18) 睡覺時**呼吸困難**	0□	1□	2□	3□	4□	5□
19) 睡覺時**用口呼吸**	0□	1□	2□	3□	4□	5□
20) 睡覺時**短暫性地停止呼吸 (至少有幾秒鐘)**	0□	1□	2□	3□	4□	5□
21) 睡覺時試過**咀唇變藍**	0□	1□	2□	3□	4□	5□
22) 睡覺時，經常『**反瞓**』(即**經常轉身**)	0□	1□	2□	3□	4□	5□
23) 以特殊『**俯睡**』的姿勢睡覺 (即**趴喺度瞓，面部向下，頸部伸長，臀部翹起**)	0□	1□	2□	3□	4□	5□
24) 睡覺時『**磨牙**』	0□	1□	2□	3□	4□	5□
25) 睡覺時『**瀨尿**』	0□	1□	2□	3□	4□	5□
26) 睡覺時『**發開口夢**』	0□	1□	2□	3□	4□	5□
27) 睡覺時**發惡夢**	0□	1□	2□	3□	4□	5□
28) 早上太早醒來後 (如天還沒亮)，便不能再入睡	0□	1□	2□	3□	4□	5□
29) 早上起床後，覺得**口乾**	0□	1□	2□	3□	4□	5□
30) 早上**很不願意起床**	0□	1□	2□	3□	4□	5□
31) 早上起床後，覺得**好像沒有休息過**	0□	1□	2□	3□	4□	5□
32) 早上起床後，覺得**頭痛**	0□	1□	2□	3□	4□	5□
33) 白天裡，覺得**好疲倦**	0□	1□	2□	3□	4□	5□

34) a. 在過往一年內，他/她有沒有**打鼻鼾**呢?

0□ 從不 (跳至35題)　1□ 每月少於一晚　2□ 每月有一至兩晚
3□ 每週有一至兩晚　4□ 每週有三晚或以上　5□ 不清楚 (跳至35題)

b. 鼻鼾聲有幾嚴重?

1□ 輕微　2□ 一般　3□ 嚴重　4□ 非常嚴重

c. 幾多歲開始有鼻鼾聲呢? _____

35) a. 在過往一年內，他/她**睡著後**，有沒有突然間**尖叫**或**驚恐**，你嘗試叫醒他/她，卻好像沒有反應。當他/她睡醒後，對昨晚發生的事卻完全沒有印象?

0□ 沒有 (跳至36題)　1□ 每月少於一晚　2□ 一個月一至兩晚
3□ 一週有一至兩晚　4□ 一週有三晚或以上　5□ 不清楚 (跳至36題)

b. 幾多歲開始呢? _____

36) a. 他/她**睡著後**, 有沒有試過『**夢遊**』呢? (例如: **落床周圍走動**等動作)

0□ 沒有 (跳至37題) 1□ 每月少於一晚 2□ 一個月一至兩晚

3□ 一週有一至兩晚 4□ 一週有三晚或以上 5□ 不清楚 (跳至37題)

b. 「夢遊」的情況通常發生 1□ 睡了不久 2□ 睡到半夜 3□ 醒之前 4□ 整晚

c. 請形容一下「夢遊」的情況：_____

d. 「夢遊」時有沒有**弄傷自己**或**其他人**? 0□ 沒有 1□ 有

e. 幾多歲開始呢? _____

37 a. **白天裡**, 他/她有沒有**小睡(瞓晏覺/午睡)**的習慣呢?

0□ 不需要 (跳至38題) 1□ 想, 但不能睡著 (跳至38題)

2□ 每週有一至兩天 3□ 每週有三至五天

4□ 每天或差不多每天都有 5□ 不清楚 (跳至38題)

b. 他/她通常會睡多少時間?

1□ 少於15分鐘 2□ 16至30分鐘 3□ 31至60分鐘

4□ 61至120分鐘 5□ 超過120分鐘 (約:_____分鐘)

38) a. **白天裡**, 他/她有沒有在以下的情況下**突然睡著**呢?

場合	不曾發生	每月 少於一次	每月 一至兩次	每週 一至兩次	每日 一至兩次	每日幾次
看書時						
搭車或地鐵時						
站立時						
進食時						
看電視時						
上課時						

b. **白天裡**, 他/她在以下情況下會否很容易**打瞌睡（眼瞓）**?

	從未	偶爾	很可能	經常
i. 坐下閱讀時，便打瞌睡。				
ii. 在看電視時，便打瞌睡。				
iii. 在公眾地方（如戲院、公園）安靜坐下，便打瞌睡。				
iv. 乘坐在汽車上，連續行駛超過一小時，便打瞌睡。				
v. 在下午時舒服地躺下休息時，便打瞌睡。				
vi. 坐下與別人閒談時，便打瞌睡。				
vii. 午飯後，安靜地坐下時，便打瞌睡。				
viii. 坐在車上，當車子停在紅燈前或在塞車時，幾分鐘便打瞌睡。				

39) a. 晚上睡覺時, 家裡環境如何? 0□ 不嘈吵 1□ 有點嘈吵 2□ 非常嘈吵

40) a. 除了以上所提及, 他/她還有其他睡眠問題嗎? 0□ 沒有 1□ 有 (請列出： ___)

b. i. 家人當中有沒有任何睡眠問題呢? 0□ 沒有 1□ 有 (請答b.ii.題)

ii. 如有, 請列出問題(可 **"✓"** 多項選擇)： 1□ 經常打鼻鼾 (家人：_____)

2□ 經常失眠 (家人：_____)

3□ 其他：_____ (家人：_____)

(C) 兒童的生活習慣和健康狀況

41) 他/她**每日**平均花多少時間在以下的活動裡?

a. 上課:___小時___分鐘　b. 溫習、做功課:___小時___分鐘　c. 看電視:___小時___分鐘
d. 講電話:___小時___分鐘　e. 看課外書籍:___小時___分鐘　f. 運動:___小時___分鐘
g. 玩電子遊戲:___小時___分鐘　h. 用電腦/上網:___小時___分鐘　i. 交通:___小時___分鐘
j. 其他課外活動(不包括體育活動, 例如: 彈琴、畫畫、跳舞等): ___小時___分鐘

42) **晚上睡覺前一小時**, 他/她通常會做些甚麼事情? (可 **"✓"** 多項選擇)

1□ 溫習/做功課　2□ 看電視　3□ 運動　4□ 講電話　5□ 進食
6□ 看課外書籍　7□ 玩電子遊戲　8□ 用電腦/上網　9□ 其他: _____

43) a. 你認為他/她是否比同年齡的孩子**過度活躍**呢?　0□ 否　1□ 是
b. 他/她是否經常**發脾氣或情緒難以控制**?　0□ 否　1□ 是
c. 與上一個學年比較, 他/她在**學習上的成績表現**是怎樣?
1□ 非常差　2□ 較差　3□ 差不多　4□ 較好　5□ 非常好

44) a. 最近一年內, 他/她的**健康狀況**是怎樣呢? 1□ 非常差　2□ 差　3□ 普通　4□好　5□ 非常好
b. 最近一年內, 他/她有沒有**長期服食藥物**? 0□ 沒有　1□ 有 (請列明:_____)

45) 最近一年內, 他/她有沒有**患上**:

a.**鼻敏感**?	0□ 沒有	1□ 間中	2□ 經常
b.**鼻竇炎**?	0□ 沒有	1□ 間中	2□ 經常
c. **中耳炎**?	0□ 沒有	1□ 間中	2□ 經常

d.**哮喘**?	0□ 沒有	1□ 間中	2□ 經常
e.**扁桃腺發炎?**	0□ 沒有	1□ 間中	2□ 經常
f.**喉嚨發炎?**	0□ 沒有	1□ 間中	2□ 經常

46) a. 他/她**現在或以前**有沒有患上以下疾病? (可 "✓" 多項選擇)

0 □ 沒有　1 □ 過於肥胖　2 □ 眼疾　3 □ 膽固醇過高
4 □ 關節炎　5 □ 癲癇症　6 □ 心臟病　7 □ 癌症 (_____)
8 □ 糖尿病　9 □ 長期肺病　10□ 濕疹　11□ 精神病 / 情緒病
12□ 地中海貧血病　13□ 遺傳病 (_____)　14□ 高血壓　15□ 中風
16□ 其他 (請說明) : _____

b. 他/她的父親**現在或以前**有沒有患上以下疾病? (可 "✓" 多項選擇)

0 □ 沒有　1 □ 過於肥胖　2 □ 眼疾　3 □ 膽固醇過高
4 □ 關節炎　5 □ 癲癇症　6 □ 心臟病　7 □ 癌症 (_____)
8 □ 糖尿病　9 □ 長期肺病　10□ 濕疹　11□ 精神病 / 情緒病
12□ 地中海貧血病　13□ 遺傳病 (_____)　14□ 高血壓　15□ 中風
16□ 哮喘　17□ 鼻敏感　18□ 其他 (請說明) : _____

c. 他/她的母親**現在或以前**有沒有患上以下疾病? (可 "✓" 多項選擇)

0 □ 沒有　1 □ 過於肥胖　2 □ 眼疾　3 □ 膽固醇過高
4 □ 關節炎　5 □ 癲癇症　6 □ 心臟病　7 □ 癌症 (_____)
8 □ 糖尿病　9 □ 長期肺病　10□ 濕疹　11□ 精神病 / 情緒病
12□ 地中海貧血病　13□ 遺傳病 (_____)　14□ 高血壓　15□ 中風
16□ 哮喘　17□ 鼻敏感　18□ 其他 (請說明) : _____

d. 他/她的祖父/祖母/外祖父/外祖母**現在或以前**有沒有患上以下疾病? (可 "✓" 多項選擇)

0 ☐ 沒有　1 ☐ 過於肥胖　2 ☐ 眼疾　3 ☐ 膽固醇過高
4 ☐ 關節炎　5 ☐ 癲癇症　6 ☐ 心臟病　7 ☐ 癌症 (_____)
8 ☐ 糖尿病　9 ☐ 長期肺病　10☐ 濕疹　11☐ 精神病 / 情緒病
12☐ 地中海貧血病　13☐ 遺傳病 (_____)　14☐ 高血壓　15☐ 中風
16☐ 哮喘　17☐ 鼻敏感　18☐ 其他 (請說明) : _____

47) a. 他/她是否足月出世?　0☐ 否 (出世時: ____週)　1☐ 是
b. 他/她是否以母乳餵養?　0☐ 否　1☐ 是 (約維持: ___月)

48) 如果有需要, 你願意我們替他/她安排**睡眠檢查**和**身體檢查**嗎?　1☐ 願意　0☐ 不願意

(D) 家庭資料

49) 請填寫這兒童之父母的個人資料：

a. 父親 i. 年齡：_____
ii. 職業： 1☐ 無業　2☐ 工人　3☐ 文員　4☐ 專業人員　5☐其他: _____
iii. 教育程度(最高學歷)： 1☐ 無　2☐ 小學　3☐ 初中　4☐ 高中　5☐大學或以上

b. 母親 i. 年齡：_____
ii. 職業： 1☐ 無業　2☐ 工人　3☐ 文員　4☐ 專業人員　5☐其他: _____
iii. 教育程度(最高學歷)： 1☐ 無　2☐ 小學　3☐ 初中　4☐ 高中　5☐大學或以上

50) 父母的婚姻狀況： 1☐ 同居　2☐ 已婚　3☐ 離婚　4☐ 鰥/寡　5☐ 未婚

51) a. 有沒有人在家裡吸煙?　0☐ 沒有　1☐ 間中　2☐ 經常
b. 家裡有沒有飼養寵物?　0☐ 沒有　1☐ 有 (種類: _____ 飼養年期: ___年___月)

52) 住所類型：
1☐ 公屋　2☐ 居屋　3☐ 私人樓宇　4☐ 木屋/臨屋　5☐村屋　6☐其他: _____

53) 居住面積：
1☐ 200平方呎或以下　2☐ 201-400平方呎　3☐ 401-600平方呎　4☐ 601-800平方呎
5☐ 801-1,000平方呎　6☐ 1,001平方呎以上

54) 家庭每月總收入：
1☐ HK$5,000或以下　2☐ HK$5,001-10,000　3☐ HK$10,001-15,000　4☐ HK$15,001-20,000
5☐ HK$20,001-60,000　6☐ HK$60,001或以上　7☐ 領取綜援金(約: _____)　8☐ 不定 (約: _____)

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Original Research

SLEEP DISORDERS

Natural History of Primary Snoring in School-aged Children

A 4-Year Follow-up Study

Albert M. Li, MD; Yin Zhu, MM; Chun T. Au, MPhil; Dennis L. Y. Lee, MB; Crover Ho, RPSGT; and Yun K. Wing, MB

Background: **The objective of this study was to examine the natural history of childhood primary snoring (PS) and to identify predictive clinical symptoms and risk factors associated with PS progression to obstructive sleep apnea (OSA).**

Methods: **Children aged 6 to 13 years old who received a diagnosis of PS in our previous community-based OSA prevalence study were invited to undergo repeat polysomnography (PSG) at 4-year follow-up. Subjects with an obstructive apnea hypopnea index (OAHI) ≥ 1 were classified as having OSA at follow-up.**

Results: **Seventy children (60% boys) with a mean age of 14.7 ± 1.8 years were analyzed in this follow-up study. The mean duration of follow-up was 4.6 ± 0.6 years. At follow-up, 26 subjects (37.1%) progressed to OSA, of whom five (7.1%) had moderate to severe disease (OAHI ≥ 5). Twenty-two (31.4%) remained at PS, and 18 (25.7%) had complete resolution of their snoring with normal PSG. Persistent snoring had a positive predictive value of 47.7% and a negative predictive value of 86.4% for progression from PS to OSA. Multivariate logistic regression analysis showed that persistent overweight/obesity was a significant risk factor for the development of OSA at follow-up, with an OR of 7.95 (95% CI, 1.43-44.09).**

Conclusions: **More than one-third of school-aged children with PS progressed to OSA over a 4-year period, although only 7.1% developed moderate to severe disease. Weight control may be an important component in the management of PS because obesity was found to be a significant risk factor for PS progression.** ***CHEST 2013; 143(3):729–735***

Abbreviations: AASM = American Academy of Sleep Medicine; OAHI = obstructive apnea hypopnea index; OSA = obstructive sleep apnea; PS = primary snoring; PSG = polysomnography; SDB = sleep-disordered breathing; Spo_2 nadir = oxygen saturation nadir

Snoring is a common symptom of pediatric sleep-disordered breathing (SDB), and the reported prevalence of habitual snoring ranges from 4.0% to 34.5%.[1-4] SDB includes a spectrum of diseases with severity ranging from primary snoring (PS), to upper airways resistance syndrome, to obstructive sleep apnea (OSA).[5,6] In contrast to OSA, PS, which is defined as snoring without apnea, frequent arousals, or gas exchange abnormalities,[7] has been positioned at the milder end of the SDB severity continuum,[8] and treatment is usually not prescribed.[9]

Nevertheless, whether deferment of treatment of PS is safe has recently led to more research. Kwok et al[10] found that children with PS had increased casual daytime BP and reduced arterial distensibility. Our research group further demonstrated that nighttime BP was also elevated in children with PS.[11] A more

Manuscript received May 14, 2012; revision accepted September 15, 2012.

Affiliations: From the Department of Pediatrics (Dr Li, Ms Zhu, and Mr Au), the Department of Otorhinolaryngology - Head and Neck Surgery (Dr Lee), and the Department of Psychiatry (Mr Ho and Dr Wing), Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong.

Drs Li and Zhu are the joint first authors of this manuscript.

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Correspondence to: Albert M. Li, MD, Department of Pediatrics, 6th Floor, Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong; e-mail: albertmli@cuhk.edu.hk

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recent study found that PS was a risk factor for hyperactive and inattentive behavior and poor school performance in children.[12] Accumulating evidence suggests PS may be associated with a variety of clinical sequelae, and, therefore, it should no longer be considered as completely benign.[13]

Another important issue that relates to whether PS, if left untreated, progresses to OSA, persists, or resolves over time has been poorly investigated. To our knowledge, only three research studies that examined the natural history of PS in children have been published. The three studies repeated polysomnography (PSG) in cohorts of 20, nine, and 31 children with PS over a 2-year, 3-year, and 6-month period, respectively. All three studies concluded that PS in children generally did not evolve to OSA over time.[14-16] These studies, however, had small sample sizes and consisted of hospital-based subjects. In this study, we aimed to determine (1) the natural history of PS in school-aged children recruited from the community over a 4-year period and (2) the clinical symptoms and risk factors predictive of PS progression to OSA.

Materials and Methods

Subjects

This was a prospective study of a cohort established between 2003 and 2005 for a childhood OSA epidemiologic study.[17] Children aged 6 to 13 years old from 13 primary schools were randomly recruited. A total of 619 subjects underwent PSG, and 161 were defined as having PS (see later discussion in the "Polysomnography" section for definition). For this follow-up study, as a result of limited resources, only the first 99 consecutive subjects with PS were invited to undergo repeat assessment. Subjects were excluded from the study if they had cardiovascular, renal, or neuromuscular diseases; chromosomal abnormalities; or acute illness within 2 weeks of PSG; or if they had undergone upper airway surgery or had started on CPAP treatment during the follow-up period. Written informed consent and assent were obtained from the parents and subjects, respectively. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (CRE_2007.363).

Sleep Symptom Questionnaire

A validated sleep symptom questionnaire[18] was completed by parents of recruited subjects at baseline and follow-up, and the following information was extracted: (1) snoring frequency and other sleep-related symptoms rated on a 6-point scale (0 = never, 1 = less than 1 night per month, 2 = 1 to 2 nights per month, 3 = 1 to 2 nights per week, 4 = 3 nights or more per week, 5 = unclear), snoring and other OSA-related symptoms were defined as present if their frequency scored 2 to 4; (2) clinical features: history of allergic rhinitis and asthma; and (3) socioeconomic and environmental factors. We defined "persistent" as having a positive history at both time points.

Anthropometry Assessment

The weight, height, and Tanner stage of all subjects were assessed on the day of PSG. BMI was calculated as weight/height^2 (kg/m^2). Weight, height, and BMI were converted to z scores appropriate for age and sex, according to local reference.[19] Overweight and obese children were defined as those having a BMI z score ≥ 1.036 and 1.645, corresponding to the 85th and 95th percentile, respectively. We defined "persistent overweight/obesity" as being overweight or obese at both baseline and follow-up. Pubertal stage was evaluated using a self-assessment questionnaire to categorize Tanner stages.[20] Prepubertal was defined as Tanner stage 1, and pubertal was defined as Tanner stage 2 or greater.

Tonsil and Adenoid Size Assessment

The examination was carried out in the morning after overnight PSG by an otorhinolaryngologist. The tonsils and adenoids were evaluated for size by a 4-mm rigid rhinoscope (Storz endoscopy) and a flexible laryngoscope (P4, Olympus), respectively. The sizes of tonsils and adenoids were reported as percentages of the oropharyngeal and nasopharyngeal airways, respectively. A large tonsil or adenoid was defined as the soft tissue occupying $\geq 50\%$ of the corresponding airway. Tonsils and adenoids were further classified as "persistently large" if they were large at both time points.

Polysomnography

All recruited children underwent initial and follow-up standard overnight PSG at a dedicated sleep laboratory with CNS 1000P polygraph (CNS, Inc). In brief, the central and occipital EEG, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram, and ECG were recorded. The positions of the subject, respiratory airflow (nasal cannula connected to pressure transducer), respiratory efforts (strain gauge), and arterial oxyhemoglobin saturation (by Ohmeda 3700 pulse oximeter) were measured. All data were scored by experienced PSG technologists. At baseline, the standard criteria described in our previous publication were used for scoring,[21,22] whereas at follow-up, the new American Academy of Sleep Medicine (AASM) 2007 pediatric PSG scoring criteria were used.[23] Therefore, all the baseline data of subjects with PS who participated in our follow-up study were rescored using AASM criteria. Those who were not classified as having PS by the new criteria were excluded.

The obstructive apnea hypopnea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. The oxygen desaturation index was defined as the total number of dips in arterial oxygen saturation $> 3\%$ per hour of sleep. The oxygen saturation nadir (Spo_2 nadir) was also noted. The arousal index was defined as the total number of arousals per hour of sleep.

Children who snored were given a diagnosis of PS if their OAHI was < 1 and Spo_2 nadir was $\geq 90\%$. At follow-up, children were given a diagnosis of OSA if their OAHI was ≥ 1. Normal subjects were defined as nonsnorers with an OAHI < 1 and Spo_2 nadir $\geq 90\%$.

Statistical Analysis

Student t tests, Mann-Whitney U tests, and χ^2 tests for parametric, nonparametric, and categorical data, respectively, were used to detect difference between subjects who participated in this study and those who did not. Paired t tests, Wilcoxon signed rank tests, and McNemar tests for parametric, nonparametric, and categorical data, respectively, were used to examine intragroup differences between baseline and follow-up. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio, together with their 95% CIs of OSA-related symptoms, were calculated using an online software (http://vassarstats.net/clin1.html). Binary logistic regression analyses were performed separately to investigate the factors

associated with the progression of PS to OSA and the resolution of PS to normal at follow-up. All statistical analyses were performed using SPSS 16.0 (IBM), and a P value $< .05$ was considered statistically significant.

Results

Of the 99 subjects invited, we failed to contact six and 18 refused to participate. One case subject who had received a tonsillectomy for recurrent tonsillitis during the follow-up period was excluded. Therefore, 74 subjects with PS participated in this follow-up study. There were no significant differences in demographic, clinical, environmental, socioeconomic, or polysomnographic characteristics between the 74 who participated and the 87 who did not (Table 1). Four participants had an OAHI ≥ 1 at baseline using AASM 2007 criteria during rescoring, so a total of 70 subjects were included in the final analysis. The mean time of reevaluation was 4.6 ± 0.6 years (range, 3.4-6.2 years) after the initial assessment.

Subjects' Characteristics at Baseline and Follow-up

Changes in anthropometric and PSG parameters for the whole group over the follow-up period are shown in Table 2. As expected, subjects showed a significant increase in weight and height; however, their average BMI z scores remained unchanged. The proportion of pubertal children increased from 12.9% to 100%. Only six subjects had large tonsils at baseline, of whom three had persistently large tonsils at follow-up. Three subjects had large adenoids at baseline but none at follow-up. None of the subjects had new onset of large tonsils or adenoids at follow-up. The OAHI, arousal index, and oxygen desaturation index increased, whereas the Spo_2 nadir decreased significantly over the follow-up period (Fig 1, Table 2).

Twenty-six of the 70 subjects (37.1%) developed OSA at follow-up. Their median OAHI was 2.05 (range, 1.00-13.01), and five subjects (7.1%) had an OAHI ≥ 5. Among the remaining subjects without OSA at follow-up, 22 (31.4%) remained as PS and 18 (25.7%) became normal. Four subjects were unclassified at follow-up, of whom two had an OAHI < 1 but unclear snoring status and two had an OAHI < 1 but a Spo_2 nadir $< 90\%$.

Predictive Clinical Symptoms and Risk Factors for PS Progression to OSA

Among the OSA-related clinical symptoms, only persistent snoring was significantly different between those who did and did not develop OSA at follow-up ($P = .007$). Persistent snoring had a relatively high sensitivity (87.5%; 95% CI, 66.5%-96.7%) and negative predictive value (86.4%; 95% CI, 64.0%-96.4%) despite poor specificity (45.2%; 95% CI, 30.2%-61.2%) and positive predictive value (47.7%; 95% CI, 32.7%-63.1%) for the development of OSA. The positive likelihood ratio and negative likelihood ratio of persistent snoring were 1.60 (95% CI, 1.17-2.19) and 0.28 (95% CI, 0.09-0.84), respectively, for the development of OSA.

We analyzed the effects of several potential factors in predicting progression, persistence, or resolution of PS using logistic regression models (Table 3). In identifying the risk factors for worsening of PS, the univariate analysis showed that only the presence of persistent overweight/obesity was significantly associated with progression to OSA, with an OR of 7.33 (95% CI, 1.41-38.13). In a multivariate model adjusted for baseline age, sex, persistently large tonsils, and persistent snoring, the presence of persistent overweight/obesity remained the only significant predictor,

Table 1—*Characteristics of Children With PS Who Did and Did Not Participate in the Follow-up Study*

Characteristic	Participants (n = 74)	Nonparticipants (n = 87)	*P* Value
Age, mean (SD), y	10.1 (1.7)	10.3 (1.7)	.52
Male sex	50 (67.6)	55 (63.2)	.56
Weight, mean (SD), kg	34.5 (9.7)	35.2 (10.4)	.65
Height, mean (SD), cm	137 (11.2)	139 (11.2)	.25
BMI, mean (SD), kg/m^2	18.0 (3.1)	17.9 (3.3)	.74
BMI z score, mean (SD)	0.47 (0.95)	0.38 (1.08)	.52
Puberty	13 (17.6)	17 (19.5)	.75
Large tonsils	7 (9.5)	13 (14.9)	.29
Large adenoids	3 (4.1)	6 (6.9)	.43
Snoring			.52
Sometimes	19 (25.7)	20 (23.5)	
Often	30 (40.5)	30 (34.5)	
Frequently	25 (33.8)	37 (42.5)	
Allergic rhinitis	62 (83.8)	67 (77.0)	.28
Asthma	11 (14.9)	9 (10.3)	.39
Household smoking	16 (21.6)	28 (32.2)	.13
Share bedroom with others	58 (78.4)	62 (71.3)	.30
Share bed with others	17 (23.0)	25 (28.7)	.41
Household area < 50 m^2	43 (58.1)	56 (64.4)	.42
Family income			.09
$\leq$ HK$10,000	14 (18.9)	29 (33.3)	
HK$10,001-$20,000	45 (60.8)	47 (54.0)	
$>$ HK$20,000	15 (20.3)	11 (12.6)	
Paternal education			.58
Primary or below	7 (9.5)	13 (14.9)	
Secondary	56 (75.7)	62 (71.3)	
Tertiary or above	11 (14.9)	12 (13.8)	
Maternal education			.81
Primary or below	9 (12.2)	10 (11.5)	
Secondary	55 (74.3)	68 (78.2)	
Tertiary or above	10 (13.5)	9 (10.3)	
OAHI, median (IQR), per h	0.12 (0.00-0.46)	0.15 (0.00-0.50)	.63
Spo_2 nadir, median (IQR), %	93 (92-95)	93 (92-94)	.67

Data are presented as No. (%) unless indicated otherwise. HK = Hong Kong; IQR = interquartile range; OAHI = obstructive apnea hypopnea index; PS = primary snoring; SpO_2 nadir = oxygen saturation nadir.

Table 2—*Anthropometric and Polysomnographic Data of the Subjects (N = 70) at Baseline and Follow-up*

Characteristic	Baseline	Follow-up	*P* Value
Age, y	10.2 (1.7)	14.7 (1.8)	< .001
Weight, kg	35.0 (9.7)	55.7 (13.2)	< .001
Weight *z* score	0.36 (0.96)	0.59 (1.02)	< .01
Height, cm	138 (11.5)	162 (8.8)	< .001
Height *z* score	−0.02 (1.11)	0.35 (1.27)	.01
BMI, kg/m^2	18.2 (3.1)	21.1 (3.9)	< .001
BMI *z* score	0.50 (0.94)	0.53 (0.90)	.68
Tanner stage, No. (%)			< .001
Tanner 1	61 (87.1)	0 (0)	
Tanner 2	5 (7.1)	9 (12.9)	
Tanner 3	3 (4.3)	25 (35.7)	
Tanner 4	1 (1.4)	32 (45.7)	
Tanner 5	0 (0)	4 (5.7)	
Large tonsils, No. (%)	6 (8.6)	3 (4.3)	.49
Large adenoids, No. (%)	3 (4.3)	0 (0)	.25
Sleep efficiency, median (IQR), %	86.0 (77.4-89.2)	87.0 (77.0-92.2)	.54
Sleep latency, median (IQR), min	15 (8-24)	12 (9-17)	.01
REM latency, median (IQR), min	132 (96-168)	93 (75-171)	.13
Stage N1, % TST	7.1 (2.8)	8.5 (3.9)	< .01
Stage N2, % TST	46.2 (6.2)	48.7 (6.0)	< .01
SWS, % TST	25.1 (5.8)	21.4 (6.4)	< .001
REM, % TST	20.2 (4.3)	21.4 (4.1)	.04
OAHI, median (IQR), per h	0.25 (0-0.61)	0.50 (0.08-1.50)	< .001
Spo_2 nadir, median (IQR), %	93 (92-95)	93 (91-94)	.04
ArI, median (IQR), per h	5.5 (4.6-7.5)	6.7 (5.1-8.7)	.03
ODI, median (IQR), per h	0.12 (0-0.35)	0.19 (0-0.59)	< .01

Data are presented as mean (SD) unless indicated otherwise. ArI = arousal index; ODI = oxygen desaturation index; REM = rapid eye movement; SWS = slow-wave sleep; TST = total sleep time. See Table 1 legend for expansion of other abbreviations.

with an OR of 7.95 (95% CI, 1.43-44.09). In contrast, no factors were found to be significantly associated with remission of PS.

Discussion

In this community-based follow-up study of children with PS, we demonstrated that more than one-third of the subjects progressed to OSA over a period of 4 years. Persistent snoring had a relatively high negative predictive value for PS progression. Persistent overweight/obesity placed children with PS at an increased risk of such progression. To our knowledge, this study on the natural history of PS in children is the first to report a significant proportion of subjects with disease progression to OSA and its associated risk factors.

Studies examining the natural history of PS in both adults and children are scarce. A comparison between our study and the other three published pediatric studies is shown in Table 4. None of the previous studies found significant changes in respiratory parameters for the group as a whole, and the proportion of subjects who progressed to OSA was much lower than in our study.[14-16] One possible explanation for this discrepancy is our longer follow-up period, which would allow subjects greater exposure time to the risk factor(s) leading to disease progression. One such risk factor was persistent overweight/obesity, which is understandable because obesity is a well-established risk factor for OSA.[17,24] Our current study provided robust evidence that obesity is a significant risk factor in causing disease progression along the SDB severity spectrum in children. Therefore, weight reduction may play an important role in preventing PS from progressing to OSA for overweight/obese children. However, in our study cohort the overall magnitude of change in BMI *z* score was only moderate, and we were unable to demonstrate a significant association between change in BMI *z* score and progression of PS. Further intervention to verify this hypothesis is needed.

The age range in our study was older than those of the other series. At follow-up, all of the subjects had reached puberty. However, we failed to find a significant effect of puberty on PS progression. Previous studies showed that the apnea hypopnea index had no correlation with Tanner stage in healthy adolescents.[25] It has also been suggested that changes in sex hormones were not a primary modulator of upper airways function during transition from childhood to adulthood.[26] Thus, the role of puberty in SDB remains undefined at present. On a similar note, we failed to

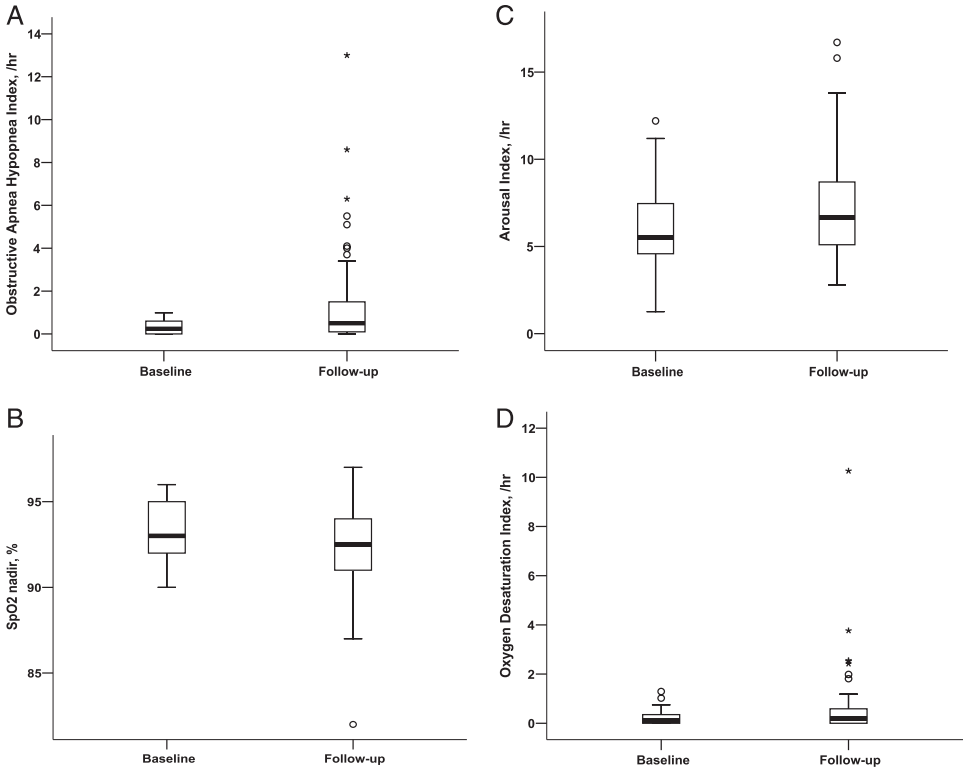

FIGURE 1. Changes in subject measurements over the follow-up period. A, Obstructive apnea hypopnea index. B, SpO_2 nadir. C, Arousal index. D, Oxygen desaturation index. SpO_2 nadir = oxygen saturation nadir.

identify sex as a significant risk factor for PS progression in the current study.

A discrepancy also exists in the percentage of resolved PS across the four studies (Table 4), likely a result of different definitions used for PS resolution. All three published studies used only decreased questionnaire-based symptom scores to define resolution of PS. We, however, classified resolution of PS as an absence of

Table 3—*Logistic Regression Analysis Assessing the Potential Factors Associated With the Worsening or Remission of PS*

	PS at Follow-up vs OSA at Follow-up		PS at Follow-up vs Normal at Follow-up	
Potential Factors	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Male sex	2.25 (0.69-7.32)	Not significant	0.64 (0.18-2.25)	Not significant
Baseline variables				
Age	0.91 (0.65-1.29)	Not significant	0.76 (0.50-1.15)	Not significant
BMI *z* score	1.40 (0.75-2.64)	…	1.18 (0.59-2.36)	…
Overweight/obesity	3.40 (0.97-11.98)	…	0.77 (0.18-3.21)	…
Tanner stage	0.46 (0.11-1.90)	…	0.73 (0.30-3.21)	…
Large tonsils	2.74 (0.26-28.41)	…	0.38 (0.03-4.58)	…
Large adenoids	Not significant	…	Not significant	…
Allergic rhinitis	0.43 (0.10-1.91)	…	0.37 (0.04-3.93)	…
Asthma	0.38 (0.06-2.28)	…	1.18 (0.29-11.04)	…
Change over follow-up period				
Change in BMI *z* score	1.00 (0.41-2.43)	…	1.40 (0.54-3.59)	…
Persistent overweight/obesity	7.33 (1.41-38.13)	7.95[a] (1.43-44.09)	0.80 (0.10-6.32)	Not significant[b]
Persistent non-overweight/obesity	0.71 (0.23-2.23)	…	0.60 (0.17-2.18)	…
Persistently large tonsils	Not significant	Not significant	Not significant	Not significant
Persistent snoring	Not significant	Not significant	…	…

OSA = obstructive sleep apnea. See Table 1 legend for expansion of other abbreviations.

[a]Adjusted for baseline age, sex, persistently large tonsils, and persistent snoring.

[b]Adjusted for baseline age, sex, and persistently large tonsils.

Table 4—*Comparison of Our Findings and Previous Studies on Natural History of PS in Children*

Comparisons	Li et al	Marcus et al[14]	Topol and Brooks[16]	Nieminen et al[15]
No. subjects with PS who underwent repeat PSG	70	20	9	31
Age at initial assessment, mean ± SD, y	10.2 ± 1.7	6 ± 4	7.2 ± 2.4	6.0 ± 1.8
Male sex, No. (%)	42 (60.0)	12 (60)	5 (55.5)	17 (54.8)
Follow-up period, mean, y	4.6	2	3.2	0.5
Baseline BMI, mean ± SD	18.2 ± 3.1	17.6 ± 4.3	NA	NA
Change in BMI *z* score	Not significant	Not significant[a]	NA	NA
Change in PSG parameters	Significant	Not significant	Not significant	Not significant
Progression to OSA, No. (%)	26 (37.1)	2 (10)	1 (11.1)	1 (3.2)
Resolution of PS, No. (%)	18 (25.7)	2 (10)	5 (38.4)[b]	16 (43.2)[c]

NA = not available; PSG = polysomnography. See Table 1 and 3 legends for expansion of other abbreviations.
[a]Change in BMI.
[b]Thirteen subjects completed sleep questionnaires.
[c]Thirty-seven subjects (31 primary snorers and six children with mild OSA) completed sleep questionnaires.

snoring together with normal PSG findings. Adenotonsillar hypertrophy was not found to be associated with PS progression in this study. It may be because the mean age of our cohort at baseline and at follow-up were both beyond the peak age of lymphoid hypertrophy.[27] However, these data were not fully analyzed in the previous studies, which included younger participants (Table 4).

In school-aged children, PS does not necessarily remain stable, especially in those who remain overweight or obese. Moreover, the presence of persistent snoring can be used as a guide for disease progression. Persistent snoring has a relatively high negative predictive value for the development of OSA, meaning that if a child with PS does not continue to snore it is less likely that he/she will develop OSA. Thus, a physician could give priority for repeat assessment to children with PS who remain overweight or obese and/or to those with persistent snoring.

This study had a few limitations. Firstly, esophageal pressure monitoring was not used; thus, cases with upper airways resistance syndrome would have been missed. Nevertheless, nasal pressure was monitored in our study, which made up to some extent for this potential source of error. Secondly, other potential factors associated with the progression or resolution of PS, such as change in craniofacial structure or fat deposition in the upper airways, were not assessed in this study.

Conclusions

In summary, more than one-third of children with PS progressed over a 4-year period to the development of OSA, and persistent overweight/obesity was a significant risk factor. Therefore, in the management of school-aged children with PS, greater attention should be paid to weight control. Because accumulating evidence suggests PS is also associated with important sequelae, further studies should examine the potential beneficial effects of intervention for this common pediatric problem.

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Dr Li: contributed to the project planning, recruitment of subjects, revision of the article, and approval of the final manuscript.
Ms Zhu: contributed to the data analysis, revision of the article, and approval of the final manuscript.
Mr Au: contributed to the performance and scoring of the polysomnography, revision of the article, and approval of the final manuscript.
Dr Lee: contributed to the performance and assessment of the otorhinolaryngology, revision of the article, and approval of the final manuscript.
Mr Ho: contributed to the performance and scoring of the polysomnography, revision of the article, and approval of the final manuscript.
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 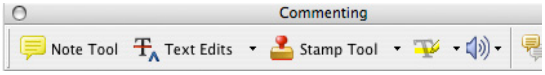

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 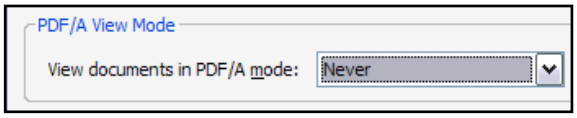

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 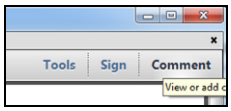

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 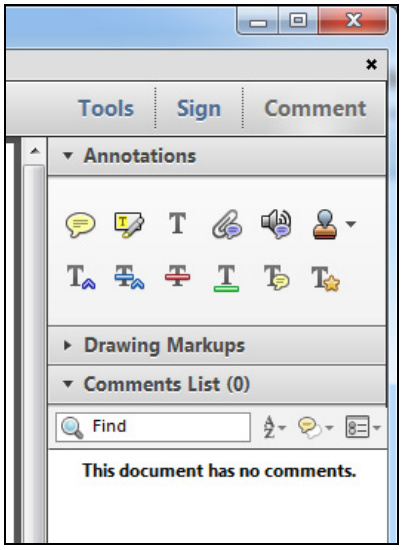
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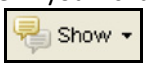
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Effects of Passive Smoking on Snoring in Preschool Children

Zhu Yin, MM[1], Au Chun Ting, MPhil[1], Leung Ting Fan, MD[1], Wing Yun Kwok, MB[2], Lam Christopher Wai Kei, PhD[3], and Li Albert Martin, MD[1]

Objective To examine the association between passive smoking and snoring in preschool children using parent-reported questionnaires and urine cotinine levels.

Study design This was a population-based cross-sectional survey of 2954 children aged 2-6 years in Hong Kong. Parent-reported questionnaires provided information on snoring and household smoking. One-third of children randomly chosen from the cohort provided urine samples for cotinine analysis. Increased urine cotinine was defined as urinary cotinine concentration ≥30 ng/mg creatinine. Using multivariate logistic regression analysis, we analyzed the association between snoring and passive smoking, controlling for potential confounders including age, sex, body mass index z-score, atopic diseases, recent upper respiratory tract infection, parental allergy, parental education, family income, and bedroom-sharing.

Results A total of 2187 completed questionnaires were included in the final analysis, and 724 children provided urine samples for cotinine measurement. After adjustment for confounding factors, questionnaire-based household smoking (>10 cigarettes/d: OR = 2.22, 95% CI = 1.02-4.81) and increased urine cotinine (OR = 4.37, 95% CI = 1.13-16.95) were significant risk factors for habitual snoring (snoring ≥3 nights per week). For occasional snoring (snoring 1-2 nights per week), reported household smoking (1-10 cigarettes/d: OR = 1.41, 95% CI = 1.14-1.76; >10 cigarettes/d: OR = 1.56, 95% CI = 1.05-2.31), and increased urine cotinine (OR = 1.82, 95% CI = 1.03-3.20) were also identified as significant risk factors. A dose-effect relationship was found for snoring frequency and adjusted natural logarithms of urinary cotinine concentrations ($P < .001$).

Conclusions Environmental tobacco smoke exposure is an independent risk factor for snoring in preschool children. Parents' smoking cessation should be encouraged in management of childhood snoring. *(J Pediatr 2013;■:■-■).*

Snoring is the most common manifestation of sleep-disordered breathing (SDB). In children, snoring has been demonstrated to be associated with neurobehavioral impairment[1-3] and cardiovascular morbidities.[4,5]

Exposure to environmental tobacco smoke is associated with respiratory tract diseases in preschool children.[6-8] Studies that examined the relationship between parental smoking and snoring in preschoolers have provided conflicting results.[9-14] Moreover, the assessment for environmental tobacco smoke exposure in almost all of the previous publications was based on parent-completed questionnaires. Hence, there is a possibility of under-reporting by parents who smoke. Additionally, it may be difficult to take into account other important factors for environmental tobacco smoke exposure such as proximity to smokers, home ventilation, and exposure occurring outside the home in a questionnaire-based survey. An objective indicator is therefore needed to enhance the reliability of assessing environmental tobacco smoke exposure. Cotinine, a major degradation product of nicotine metabolism, has become an important biomarker for quantifying passive exposure to cigarette smoke.[15] Urine cotinine is a noninvasive and commonly used objective tool in quantifying environmental tobacco smoke exposure.

In this cross-sectional community-based study, we aimed to examine the association between passive smoking and snoring in preschool children, using both parent-completed questionnaires and urine cotinine concentrations for assessment of environmental tobacco smoke exposure.

Methods

Healthy Chinese preschool children aged 2-6 years who are Hong Kong permanent residents were eligible for inclusion. Children were excluded from the study if they had premature birth at <37 weeks gestation, cardiac, renal, or neuromuscular diseases, chromosomal abnormalities, or had previously undergone upper airway surgery.

BMI	Body mass index
SDB	Sleep-disordered breathing

From the Departments of [1]Pediatrics and [2]Psychiatry, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong; and [3]The Macau Institute for Applied Research in Medicine and Health, Faculty of Health Sciences, Macau University of Science and Technology, Taipa, Macau

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The methodology and sampling frame of this study were described in our recent study.[16] Briefly, all nurseries and kindergartens registered under the Education Bureau were stratified according to the 4 geographic regions in Hong Kong and were randomly recruited in proportion to the childhood population of the respective region according to 2006 population by-census statistics. All subjects were recruited within class as a clustered randomized sampling frame. Consequently, a total of 21 kindergartens/nurseries were recruited. Parent-reported questionnaires were delivered to parents of 2954 children. Written informed consent and assent were obtained from 1 parent per subject and subjects, respectively. Approval was obtained from the Clincial Research Ethics Committee of the Chinese University of Hong Kong.

An expanded version of a validated sleep pattern and symptom questionnaire[17] was completed by 1 of the parents of recruited subjects. The question on snoring was "Does your child snore when he/she is asleep?" and the options given were "never," "only when he/she suffers from a cold or allergies," "sometimes" and, "almost always/always." For the participants who chose the latter 2 options, a drop-down list of frequencies was then provided. We defined habitual and occasional snoring as snoring ≥3 nights per week and 1-2 nights per week, respectively. Nonsnorers were defined as those reporting "never" or "only when he/she suffers from a cold or allergies." The Chinese version of the modified International Study of Asthma and Allergies in Childhood questionnaire was also given to parents for completion.[18] A question about household smoking, ie, the number of cigarettes smoked daily by people living with the child (nil; <10 cigarettes; 10-20 cigarettes; >20 cigarettes) was asked.

Anthropometry Assessment

At each participating kindergarten, a team of research assistants conducted on-site weight and height measurements. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and values were converted to z-scores appropriate for age and sex, according to local reference.[19]

Measurement of Urinary Cotinine

One-third of children who completed both questionnaires were randomly selected to provide urinary samples for cotinine analysis. The sample was collected on-site by our researchers. Urine was stored at −20°C until analysis for cotinine by enzyme-linked immunosorbent assay (Calbiotech, Spring Valley, California). The detection limit of this assay was 1 ng/mL. The inter-assay coefficients of variation were <6%. Urine cotinine concentrations were corrected for creatinine, which was measured by modified Jaffe reaction (Roche Diagnostics GmbH, Mannheim, Germany). Increased urine cotinine was defined as urinary cotinine concentrations ≥ 30 ng/mg creatinine.[20]

Statistical Analyses

For comparisons between 3 independent groups, Kruskal–Wallis tests and χ^2 tests were used for continuous and categorical data, respectively. Subsequently, Mann-Whitney tests and multiple χ^2 tests with adjusted P values (significant at $P <$ .016) were used for corresponding post hoc pairwise comparisons, respectively. Multiple logistic regression analyses were performed to investigate the association between passive smoking and snoring, adjusted for possible confounding factors. ANCOVA was used to examine the trend and differences in logarithmically transformed urinary cotinine concentrations (natural log [x + 0.1]) among different snoring frequency groups, after controlling for possible confounders. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, Illinois), and a P value of <.05 was considered statistically significant.

Results

Of a total of 2954 children recruited, 2197 questionnaires were returned, giving a response rate of 74.4%. Ten subjects with missing information on snoring were excluded, leaving 2187 children for final analysis. Of the whole group, 2085 subjects also completed the modified International Study of Asthma and Allergies in Childhood questionnaire.

There were 120 habitual snorers, 974 occasional snorers, and 1093 nonsnorers. Urine cotinine analysis was performed in 724 children (363 nonsnorers, 324 occasional snorers, and 37 habitual snorers). There were no significant differences in age, sex, BMI z-score, family income, presence of atopic diseases, household smoking, and snoring frequency distribution between those who did and did not provide urine sample. Possible risk factors for snoring were compared between different snoring groups (Table I). The reported number of cigarettes smoked daily by family members who lived with the child had a dose-response relationship with snoring frequency. However, the urine cotinine concentration did not exhibit similar relationship.

Table II shows the results of logistic regression model analyzing the association between habitual snoring and passive smoking. With reference to the nonsnoring group, questionnaire-based presence of household smoking was found to be a significant risk factor for habitual snoring either by univariate or multivariate model adjusted for age, sex, BMI z-score, presence of allergic rhinitis, asthma, eczema, upper respiratory tract infection during past 4 weeks, parental allergy, parental education, bedroom-sharing, and family income. Although increased urine cotinine was not associated with development of habitual snoring in univariate model, its adverse effect became significant after controlling for the confounders.

These analyses were repeated for occasional snoring, and both reported household smoking and increased urine cotinine were identified as significant risk factors for occasional snoring (Table II).

After logarithmic transformation, a significant increasing trend for ln urine cotinine concentrations across snoring frequency was observed ($P < .001$, Figure 1), which provided strong evidence for exposure to environmental tobacco smoke as a risk factor for snoring.

Table I. Characteristics of all subjects and distribution of variables according to snoring status

	All	Nonsnorers	Occasional snorers	Habitual snorers	*P* value
Age†,‡					.001
2 y (%)	14.0	14.8	13.2	12.5	
3 y (%)	29.3	29.3	30.4	20.0	
4 y (%)	27.6	29.3	26.2	24.2	
5 y (%)	24.2	22.4	25.5	30.8	
6 y (%)	4.9	4.2	4.7	12.5	
Male sex (%)*	53.3	50.3	55.9	60.0	.013
BMI z-score*	0.22 (–0.44 to 0.92)	0.16 (–0.47 to 0.84)	0.27 (–0.39 to 0.99)	0.18 (–0.61 to 1.20)	.047
Monthly family income (%)					.175
<10 000$HK	24.5	25.0	24.6	18.6	
10 000-50 000$HK	69.0	67.6	69.6	77.1	
>50 000$HK	6.5	7.4	5.8	4.2	
Effects of passive smoking on snoring in preschool children bedroom-sharing (%)	80.3	80.8	79.4	84.2	.399
Paternal education lower than primary school (%)	14.2	15.1	13.9	9.5	.245
Maternal education lower than primary school (%)	15.9	17.1	14.8	13.8	.309
Household smoking (%)*,†					.001
No smoking	60.6	64.4	56.7	56.9	
1-10 cigarettes/d	32.0	30.0	34.3	31.0	
>10 cigarettes/d	7.5	5.6	9.0	12.1	
Urine cotinine concentration (ng/mgCr)	4.09 (1.87-10.79)	3.85 (1.86-9.63)	4.37 (1.92-12.09)	4.01 (1.74-10.74)	.395
Increased urine cotinine (%)	10.8	8.3	13.6	10.8	.073
AR (%)*,†,‡	26.6	23.5	27.7	45.7	<.001
Asthma (%)	5.3	5.3	5.1	7.8	.478
Eczema (%)†,‡	34.6	32.9	34.6	50.9	.001
URI during past 4 weeks (%)	29.3	30.3	27.5	33.6	.222
Paternal allergy (%)	34.5	32.8	35.4	42.0	.150
Maternal allergy (%)†,‡	33.1	31.9	32.2	50.9	.013

AR, allergic rhinitis; *Cr*, creatinine; *URI*, upper respiratory tract infection.
Median (IQR) and number (percentage) are presented for continuous and categorical data, respectively.
*$P < .016$, nonsnorers vs occasional snorers.
†$P < .016$, nonsnorers vs habitual snorers.
‡$P < .016$, occasional snorers vs habitual snorers.

In addition, the reported household smoking frequency showed significant positive correlation with urine cotinine concentration. Urine cotinine concentration of nonsmoking group, 1-10 cigarettes/d group and >10 cigarettes/d group were 2.81 (1.48-5.76) vs 8.36 (3.40-24.61) vs 17.83 (5.55-43.57) ($P < .001$).

Discussion

This population-based study utilized urinary cotinine together with questionnaire to examine the effects of environmental tobacco smoke on snoring in children. We demonstrated that both parent-reported household smoking and elevated concentration of urine cotinine were significant risk factors for both habitual and occasional snoring in preschool children.

If only the parent-reported questionnaire is considered, our results are consistent with several earlier studies carried out in preschoolers.[10-13] This association between passive smoking and habitual snoring has also been found in older children.[21,22] Only 1 study has utilized an objective biomarker, serum cotinine, to assess environmental tobacco smoke and its association with transient/persistent snoring in

Table II. Association between passive smoking and snoring with reference to nonsnoring

	Habitual snorers vs nonsnorers		Occasional snorers vs nonsnorers	
	Unadjusted OR (95% CI)	aOR‡ (95% CI)	Unadjusted OR (95% CI)	aOR‡ (95% CI)
Household smoking				
1-10 cigarettes/d vs no smoking	1.17 (0.76-1.79)	1.45 (0.88-2.40)	1.30† (1.07-1.57)	1.42† (1.14-1.77)
>10 cigarettes/d vs no smoking	2.45† (1.30-4.62)	2.17* (1.01-4.70)	1.83† (1.28-2.61)	1.54* (1.04-2.29)
Urine cotinine concentration	1.00 (0.98-1.02)	1.01 (0.99-1.03)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
Increased urine cotinine	1.35 (0.45-4.05)	4.30* (1.11-16.59)	1.74* (1.07-2.85)	1.84* (1.04-3.24)

*$P < .05$.
†$P < .01$.
‡Adjusted for age, sex, BMI z-score, presence of AR, asthma, eczema, URI during past 4 weeks, paternal allergy, maternal allergy, paternal education, maternal education, bedroom-sharing, and family income.

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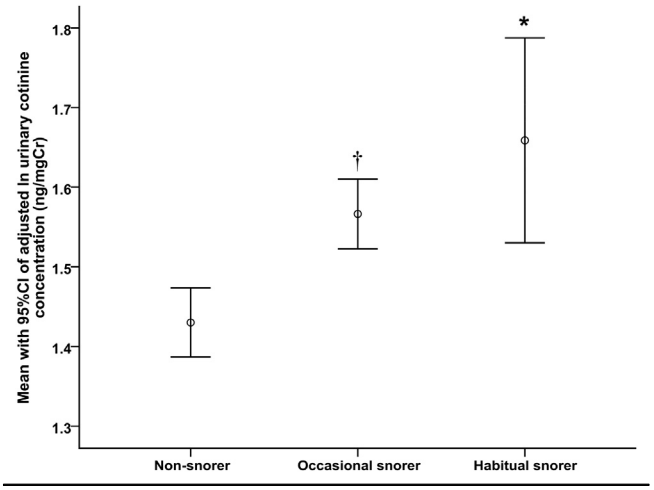

Figure. Adjusted natural logarithm urine cotinine concentrations across snoring frequency groups. The error bars show the predicted mean with 95% CI adjusted for age, sex, BMI z-score, presence of allergic rhinitis, asthma, eczema, upper respiratory tract infection during past 4 weeks, paternal allergy, maternal allergy, paternal education, maternal education, and family income. Habitual snorers ($^{*}P = .005$) and occasional snorers ($^{\dagger}P < .001$) and had significantly higher ln urinary cotinine concentrations compared with nonsnorers, respectively. *Cr*, creatinine.

children.[9] Higher cotinine levels were associated with transient/persistent snoring among non-African American children, but not in African American children. However, this interaction became insignificant when included in their full-adjusted model controlling for sex, race, socioeconomic status, birth weight, breastfeeding, and BMI z-score. Racial difference may explain the discrepancy between our finding and this study. It has been demonstrated that Americans of European and African descent differ in nicotine metabolism,[23] thus, it is reasonable to assume Chinese would have different metabolism from Caucasians. Furthermore urine cotinine may be able to discriminate between passive smokers and nonsmokers even better than cotinine in serum or saliva.[24] Together with its noninvasive collection method, urine cotinine was the most convenient and practical way to assess environmental tobacco smoke exposure in a large community-based sample.

Regarding objective evaluation of environmental tobacco smoke, we found that there were no significant differences in urine cotinine concentration between different snoring frequency groups, while interestingly, after adjustment for possible confounding factors, the presence of increased urine cotinine turned out to be a significant risk factor for both habitual and occasional snoring. The habitual snoring group included greater proportion of children with atopic diseases and parental allergy (**Table I**), thus, parents from this group may have been more likely to avoid smoking in close proximity for the sake of their children's or their own health, resulting in a lower urinary cotinine concentration than expected. In addition, the parental education levels were higher in the habitual snoring group, and parents might be more aware of the adverse effects of environmental tobacco smoke exposure. We did further analyses and found that urine cotinine concentrations were significantly lower in children with atopy (except asthma) and whose parents had allergic diseases and higher education, in spite of similar reported household smoking. Therefore, these reasons could explain why the correlation between environmental tobacco smoke exposure and snoring became significant after controlling for these confounders.

The mechanism whereby environmental tobacco smoke leads to snoring remains unclear. One study conducted in adults suggested that smoking may induce oropharyngeal narrowing and collapse through histologic changes of the uvular mucosa because of increased neurogenic inflammation.[25]

Snoring is a cardinal symptom of SDB. Accumulating evidence demonstrated that habitual snoring[1-5] and even occasional snoring[26] could be associated with a variety of adverse consequences in children, even in absence of apnea or hypopnea. Too often, clinicians may focus on surgical and medical treatment and pay insufficient attention to lifestyle modification in the management of SDB in children. Our finding that environmental tobacco smoke exposure is indeed a risk factor for snoring provides an additional reason for encouraging parents to quit smoking and provides another potential strategy for alleviating snoring in children, and may have significant clinical and public health implications.

There were several limitations in our study. First is the lack of objective measurement for snoring, which is a limitation shared with other community-based survey studies. No standardized definition of snoring was given to parents, and we were dependent on whatever parents meant by "snoring," which may be inconsistent because of their different understanding of snoring sound. However, as a result of restricted resources, overnight monitoring to record snoring was less practical for a large population survey. Second, cotinine has a half-life of about 20 hours and in urine can be detected for up to approximately 72 hours.[15] We did not record the time interval between urine sampling and last environmental tobacco smoke exposure. Hence, if a smoking parent happened not to smoke in the 72 hours prior to urine collection, then the result would have been an underestimation. However, this was less likely because overall the parent-reported smoking and the urine cotinine concentration correlated well.

In conclusion, we have provided evidence suggesting exposure to environmental tobacco smoke, examined by both questionnaire and measurement of urine cotinine, was an independent risk factor for snoring in preschool children. Further prospective studies investigating the causal relationship between passive smoking and snoring and the underlying mechanisms are needed. This issue may have important clinical implications that the risk of

snoring may be lessened by reducing environmental tobacco smoke exposure. ■

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Reprint requests: Zhu Yin, MM, Department of Pediatrics, Prince of Wales Hospital, 6th Floor, Clinical Sciences Building, Shatin, Hong Kong. E-mail: jodiezy@163.com

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Appendix

The Hong Kong Paediatric Sleep Survey

This survey is targeted towards caregivers of young children aged 36-72 months, to help understand sleep habits among this group of children. The data collected in this survey will be used strictly for scientific research and consumer education. It will remain confidential and will not be sold to any third party. All data will be collectively analyzed and not individually identified in any report that may be generated in the future.

If you have more than one child, please answer this survey with just one of them in mind. Please think about your child's sleep over the past 2 weeks in answering the following questions. Thank you.

1. You… (SELECT ONE)
   - ○ Have a child 36-47 months of age (3-3.99 years)
   - ○ Have a child 48-59 months of age (4-4.99 years)
   - ○ Have a child 60-72 months of age (5-6 years)
   - ○ None of the above

2. Is your child a… (SELECT ONE)
   - ○ Girl
   - ○ Boy

3. Was your child delivered by Normal Delivery (ND) or Caesarian Section (CS)? (SELECT ONE)
   - ○ Normal Delivery
   - ○ Caesarian Section

4. Was your child born pre-term/prematurely?
   - ○ No
   - ○ If Yes, what was the gestational age (no. of weeks of pregnancy) of your child, at the time of birth? _____Weeks (less than 37 weeks)

5. Was your child breast fed, bottle fed or mixed fed? (SELECT ONE)
   - ○ Breast Feed
   - ○ Bottle Feed
   - ○ Mixed Feed

6. If breast fed, how long was your child breastfed? (SELECT ONE if Question 4 was breast fed)
   - ○ Currently breastfed
   - ○ <1 month
   - ○ 1-3 months
   - ○ 4-6 months
   - ○ 7-12 months
   - ○ 13-18 months
   - ○ >18 months

7. What is the birth weight of your child? My child's birth weight was _____kg

8. What is the birth order of your child? (SELECT ONE)
   - ○ Oldest
   - ○ Middle
   - ○ Youngest
   - ○ A multiple (e.g. a twin or triplet)
   - ○ Only

9. Does your child snore during sleep? (SELECT ONE)
   - ○ Never
   - ○ Only when he/she has a cold or allergies
   - ○ Sometimes
   - ○ Almost always/Always

   My child snores _____ times per week

10. Where does your child sleep most of the time? (SELECT ONE)
    - ○ In his/her own room
    - ○ In parents' room
    - ○ In sibling's or other's room
    - ○ In another room of the house (e.g. living room)
    - ○ Other, please specify: _____

11. Does your child sleep with the room lights on or off? (SELECT ONE)
    - ○ on
    - ○ off
    - ○ Only a bed lamp or a floor/wall light is on
    - ○ No preference

12. Will the air conditioner be turned on during the summer where your child sleeps? (SELECT ONE)
    - ○ Yes
    - ○ No
    - ○ There is no air conditioner in my child's sleep place
    - ○ Only partially, once child is asleep, the air conditioner is turned off

13. Which of the following does your child sleep in most of the time? (SELECT ONE)
    - ○ Crib/Cot
    - ○ Own bed (any size)
    - ○ Parents' bed (any size)
    - ○ Bassinet
    - ○ Infant seat
    - ○ Swing
    - ○ Sarong/Hammock
    - ○ Futon/Tatami Mat on his/her own
    - ○ Futon/Tatami Mat with parents
    - ○ Other, please specify: _____

14. In what position does your child sleep most of the time? (SELECT ONE)
    - ○ On his/her tummy
    - ○ On his/her side
    - ○ On his/her back

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15. Which of the following usually occurs on most nights for your child in the hour before bedtime? (SELECT ALL THAT APPLY)
- ☐ Bath/shower
- ☐ Massage
- ☐ Read books/being read to
- ☐ Rocked
- ☐ Watch television/video
- ☐ Play video/computer games/NDS/PSP
- ☐ Have dinner or a snack
- ☐ Homework
- ☐ Have a bottle, drink, or breastfed
- ☐ Run around
- ☐ Brush teeth
- ☐ Play with favorite toys
- ☐ Cuddle
- ☐ Say prayers
- ☐ Sing songs
- ☐ Listen to music
- ☐ Practice musical instrument
- ☐ Piggy-back
- ☐ Other, please specify:_____

16. How does your child fall asleep most of the time? (SELECT ALL THAT APPLY)
- ☐ While being bottle-fed
- ☐ While being breast-fed
- ☐ While being rocked
- ☐ While being held
- ☐ While watching television/video
- ☐ While listening to a story/music
- ☐ In swing or stroller
- ☐ In sarong or hammock
- ☐ On Futon/Tatami Mat alone in the room
- ☐ On Futon/Tatami Mat and with a parent in the room
- ☐ In his/her own crib/bed alone in the room
- ☐ In parent's bed alone in the room
- ☐ In his/her own crib/bed (any size) and with a parent in the room
- ☐ In parent's bed and with a parent in the room
- ☐ In another room of the house (e.g., living room)
- ☐ Other, please specify:_____

17. In a typical 7-day week, how often does your child have the exact same nighttime before bed routine? (SELECT ONE)
- ○ Never
- ○ 1-2 nights per week
- ○ 3-4 nights per week
- ○ 5-6 nights per week
- ○ Every night

18. What time do you usually start your child's nighttime before bed routine? _____

19. What time do you usually put your child to bed at night? _____

20. Typically, how difficult is bedtime for your child, for example, fussing, crying, protesting? (SELECT ONE)
- ○ Very Easy
- ○ Somewhat Easy
- ○ Neither Easy nor Difficult
- ○ Somewhat Difficult
- ○ Very Difficult

21. How long does it typically take your child to fall asleep at night? (SELECT ONE)

EXAMPLE: If you put your child to bed at 8:15 PM and your child falls asleep at 8:30 PM, it took 15 minutes for your child to fall asleep.
- ○ Less than 5 minutes
- ○ 5-15 minutes
- ○ 16-30 minutes
- ○ 31-60 minutes
- ○ More than 1 hour

22. How often, if ever, does your child have a difficult time falling asleep at night? (SELECT ONE)
- ○ Every night
- ○ 5-6 nights per week
- ○ 3-4 nights per week
- ○ 1-2 nights per week
- ○ 1-3 nights per month
- ○ Less than once a month
- ○ Never

23. Does your child sleep with a toy or favorite blanket? (SELECT ONE)
- ○ Yes
- ○ No

24. Does your child ever sleep in your bed with you? (SELECT ONE)
- ○ Yes
- ○ No

25. How many times does your child typically wake during the night? _____ times per night

26. How often does your child wake during the night, if ever? (SELECT ONE)
- ○ Every night
- ○ 5-6 nights per week
- ○ 3-4 nights per week
- ○ 1-2 nights per week
- ○ 1-3 nights per month
- ○ Less than once a month
- ○ Never

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27. When your child wakes up during the night, what do you do? (SELECT ALL THAT APPLY)
- ☐ Pick up my child and hold/rock him/her until child falls asleep
- ☐ Pick up my child and put him/her back down while child is still awake
- ☐ Rub or pat my child but do not pick up or take out of crib/bed
- ☐ Bottle feed child back to sleep
- ☐ Breastfeed/nurse child back to sleep
- ☐ Give my child a pacifier
- ☐ Change diaper
- ☐ Comfort my child verbally but don't pick child up or take child out of crib/cotbed
- ☐ Bring my child into my bed
- ☐ Let my child cry and fall back to sleep by himself/herself
- ☐ Give my child a few minutes to see if he/she falls back to sleep
- ☐ Play with my child until child is ready to go back to sleep
- ☐ Watch television/a video with my child until he/she falls asleep
- ☐ Sing to child
- ☐ Other, please specify:_____

28. When your child wakes up during the night, how quickly do you response to him/her?
- ○ Immediately
- ○ 5-30 minutes later
- ○ ½-1 hour later
- ○ Ignore and let him/her go back to sleep by him/herself

29. On a typical night, how much total time during the NIGHT is your child awake?

_____ hours _____ minutes

EXAMPLE: If your child woke up 2 times and was awake for about 15 minutes each time, your child's total time spent awake would be 30 minutes.

30. On a typical night, what is the longest stretch of time that your child is asleep during the NIGHT without waking up?

_____ hours _____ minutes

31. What time does your child usually wake up in the morning? _____

32. How much total time does your child spend sleeping during the NIGHT (between 7 in the evening and 8 in the morning)

_____ hours _____ minutes

33. How many naps does your child take during a typical DAY? (between 8 in the morning and 7 in the evening)

_____ naps

34. How much total time does your child spend sleeping during the DAY? (between 8 in the morning and 7 in the evening)

_____ hours _____ minutes

EXAMPLE: If your child took 2 naps and slept 1 hour each time, your child's total time spent sleeping during the day is 2 hours.

35. Please rate how well your child usually sleeps at night: (SELECT ONE)
- ○ Very Well
- ○ Well
- ○ Fairly Well
- ○ Fairly Poorly
- ○ Poorly
- ○ Very Poorly

36. Do you consider your child's sleep as a problem? (SELECT ONE)
- ○ A very serious problem
- ○ A small problem
- ○ Not a problem at all

37. Are you the child's…? (SELECT ONE)
- ○ Father
- ○ Mother
- ○ Grandparent
- ○ Other, please specify: _____

38. What is your age? (SELECT ONE)
- ○ Under 21
- ○ 21-24
- ○ 25-29
- ○ 30-34
- ○ 35-39
- ○ 40-44
- ○ 45-49
- ○ 50 or older

39. Which category describes your current occupational status? (SELECT ONE)
- ○ Employed full-time
- ○ Employed part-time
- ○ On maternity leave
- ○ Homemaker/at-home parent
- ○ Student
- ○ Unemployed/in-between jobs
- ○ Other, please specify: _____

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40. What is the highest level of education you have completed? (SELECT ONE)
○ Elementary/Primary school
○ High school/Secondary school
○ Diploma/Pre–University/Junior College
○ College/University
○ Post graduate
○ Other, please specify: _____

41. What type of housing do you live in? (SELECT ONE)
○ Flat/Apartment (Government/Public)
○ Flat/Apartment/Condominium (Private)
○ House/Landed property
○ Other, please specify: _____

42. In which of the following District do you live in Hong Kong? (SELECT ONE)
○ Hong Kong Island-Central and Western
○ Hong Kong Island-Eastern
○ Hong Kong Island-Southern
○ Hong Kong Island-Wan Chai
○ Kowloon-Kowloon City
○ Kowloon-Kwun Tong
○ Kowloon-Sham Shui Po
○ Kowloon-Wong Tai Sin
○ Kowloon-Yau Tsim Mong
○ New Territories-Islands
○ New Territories-Kwai Tsing
○ New Territories-North
○ New Territories-Sai Kung
○ New Territories-Shatin
○ New Territories-Tai Po
○ New Territories-Tsuen Wan
○ New Territories-Tuen Mun
○ New Territories-Yuen Long

43. How many household memebers (in total) are living in the same household?_____

44. What is the household montly total income (HKD)? (SELECT ONE)
○ Less than10 000
○ 10 000-20 000
○ 20 000-30 000
○ 30 000-40 000
○ 40 000-50 000
○ 50 000-60 000
○ 60 000-70 000
○ Over 70 000

45. Is your child under regular follow-up with a doctor for a medical condition? (Exclude routine immunization and well-baby checkups) (SELECT ONE)
○ Yes
○ No

46. Do any of your household members smoke? (SELECT ONE)
○ Yes
○ No

47. What time do you come home from work on a normal working day?
_____

48. What time do you go to bed on a normal working day?
_____

49. Do you consider yourself have a sleep problem? (SELECT ONE)
○ A very serious problem
○ A small problem
○ Not a problem at all

50. Who is the child's primary caregiver during the day? (SELECT ONE)
○ Parent
○ Grandparent
○ Other relative
○ Other caregiver (e.g. maid, nanny)
○ Play group/kindergarden
○ Professional Daycare service
○ Other, please specify: _____

51. Where is your child usually cared for, during the day? (SELECT ONE)
○ At home
○ Outside of the home

52. Do you wish to take part in further study (joint organized by The Chinese University of Hong Kong) (SELECT ONE)
○ Yes
○ No

53. Please enter your contact numbers (OPTIONAL): _____/_____

54. Please enter your e-mail address (OPTIONAL): _____

THANK YOU FOR YOUR PARTICIPATION.

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Zhu Yin

Education

Doctor of Philosophy in Medical Sciences — Aug 2010 – Current

The Chinese University of Hong Kong, Hong Kong, China

Master of Clinical Medicine — Jul 2004 – Jul 2006

Faculty of Medicine, Fudan University, Shanghai, China

Bachelor of Clinical Medicine — Sep 1999 – Jul 2004

Faculty of Medicine, Fudan University, Shanghai, China

Award

Poster presentation award 2nd prize in Sleep 2012 - Comprehensive Workshop on Clinical Polysomnography & Conference on Sleep Medicine, Hong Kong, 2012

Publications

Accepted Manuscripts

1. Li AM, Zhu Y, Au CT, Lee DL, Ho C, Wing YK. Natural history of primary snoring in school-aged children: a 4-year follow-up study. Chest. 2013;143(3):729-735.
2. Zhu Y, Au CT, Leung TF, Wing YK, Lam CWK, Li AM. Effects of passive smoking on snoring in preschool children. J Pediatr (accepted).

Poster Presentations

1. Li AM, Zhu Y, Au CT, Kong APS, Wing YK. “Association between obstructive sleep apnoea and glucose tolerance in children and adolescents,” presented in Sleep 2012 -

Comprehensive Workshop on Clinical Polysomnography & Conference on Sleep Medicine; Hong Kong,2012

2. Li AM, Zhu Y, Au CT, Lee DL, Ho C, Wing YK. “Natural history of primary snoring in school-aged children: a 4-year follow-up study”, presented in Sleep 2012 - Comprehensive Workshop on Clinical Polysomnography & Conference on Sleep Medicine; Hong Kong,2012

3. Zhu Y, Au CT, Lam HS, Chan KCC, Ho C, Wing YK, Li AM. “Sleep architecture in school-aged children with primary snoring”, presented in Sleep 2012 - Comprehensive Workshop on Clinical Polysomnography & Conference on Sleep Medicine; Hong Kong,2012

Oral Presentations

1. Presented “Glucose tolerance in children with obstructive sleep apnea” in Joint Annual Scientific Meeting 2011 - The Hong Kong Paediatric Society & American Academy Society & Hong Kong Paediatric Nurses Association; Hong Kong, 2011

2. Presented “Association between sleep architecture and glucose tolerance in children and adolescents” in The 7th Asian Sleep Research Society Congress; Taipei, Taiwan, 2012

3. Presented “Natural history of primary snoring in school-aged children: a 4-year follow-up study” in The 7th Asian Sleep Research Society Congress; Taipei, Taiwan, 2012

Qualifications & Certifications

Summer course on “How to conduct and publish systematic reviews and meta-analyses?”, August 2011, School of Pub lic Health and Primary Care, The Chinese University of Hong Kong

Working Experiences

Resident Doctor Jul 2006 – May 2010

Children's Hospital of Fudan University, Shanghai, China